Dissertation on

A STUDY TO ANALYZE PATTERNS OF STRUCTURAL CHANGES IN CLINICALLY SIGNIFICANT DIABETIC MACULAR EDEMA ON OPTICAL COHERENCE TOMOGRAPHY

Submitted in partial fulfilment of requirements of

M.S. OPHTHALMOLOGY

BRANCH – III

REGIONAL INSTITUTE OF OPHTHALMOLOGY

MADRAS MEDICAL COLLEGE

CHENNAI- 600 003

THE TAMILNADU

DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI

APRIL 2013

CERTIFICATE

This is to certify that this dissertation entitled **"A STUDY TO ANALYZE PATTERNS OF STRUCTURAL CHANGES IN CLINICALLY SIGNIFICANT DIABETIC MACULAR EDEMA ON OPTICAL COHERENCE TOMOGRAPHY"** is a bonafide record of the research work done by **Dr. SHIVARAJ BUDIHAL,** Post graduate in Regional Institute of Ophthalmology, Madras Medical College and, Government General Hospital, Chennai-03, in partial fulfilment of the regulations laid down by The Tamil Nadu Dr.M.G.R. Medical University for the award of M.S. Ophthalmology Branch III, under my guidance and supervision during the academic years 2010-2013.

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ACKNOWLEDGEMENT

I express my sincere thanks and gratitude to **Prof. DR. V. KANAGASABAI, M.D.,** Dean, Madras Medical College for permitting me to conduct this study.

I have great pleasure in thanking professor Dr**. K. MARAGATHAM, M.S., DO.,** Director and Superintendent RIO – GOH, Madras Medical College, Chennai, for her valuable advice in preparing this dissertation.

I express my profound gratitude to **Prof . Dr. R. RAVIKUMAR M.S., D.O.,** my unit chief and my guide for his valuable guidance and constant support at every stage throughout the period of this study.

I am very grateful to my unit assistants**,Prof B.RADHAKRISHNAN M.S., D.O., Dr. A. PALANIRAJ M.S., Dr. R. PADMAPRIYA M.S.,** and **Dr. K.RAVIKUMAR, M.S.,**for rendering their valuable advice and guidance for the study.

I wish to express my sincere thanks to all the professors, assistant professors and all my colleagues who had helped me in bringing out this study.

Finally, I am indebted to all the patients for their sincere co-operation for the completion of this study.

INSTITUTIONAL ETHICS COMMITTEE
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CERTIFICATE OF APPROVAL

To
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Dear Dr. Shivaraj budihal,

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "A study to analyze patterns of structural changes in clinically significant diabetic macular edema on optical coherence tomography". No.34122012.

The following members of Ethics Committee were present in the meeting held on 11.12.2012 conducted at Madras Medical College, Chennai -3.

1.	Dr.S.K.Rajan, M.D.FRCP, DSc	--- Chairperson
2.	Prof. R. Nandhini MD Director, Instt. of Pharmacology ,MMC, Ch-3	-- Member Secretary
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8.	Thiru. S. Govindsamy. BA, BL	-- Lawyer
9.	Tmt.Arnold Saulina MA MSW	--- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

R Nandini 21/12/12
Member Secretary, Ethics Committee


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Paper ID	295342230
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Assignment title	Medical
Author	Shivaraj Budihal 22101809 M.S. Ophthalmology
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Submission time	29-Dec-2012 04:54PM
Total words	10247

First 100 words of your submission

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DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation titled "A **STUDY TO ANALYZE PATTERNS OF STRUCTURAL CHANGES IN CLINICALLY SIGNIFICANT DIABETIC MACULAR EDEMA ON OPTICAL COHERENCE TOMOGRAPHY"** is a bonfide and genuine research work carried out by me under the guidance of Prof. Dr, R . Ravikumar M.S.,D.O, Professor Department of Uvea and Retina services , Regional institiute of ophthalmology. Government Ophthalmic hospital. Chennai -600008.

Date

Place

Dr. SHIVARAJ BUDIHAL,

CONTENTS

ABBREVIATIONS

OCT	**-**	Optical coherence tomography
FFA	-	Fundus fluorescein angiography
DR	**-**	Diabetic retinopathy
NPDR	**-**	Non proliferative diabetic retinopathy
PDR	-	Proliferative diabetic retinopathy
WESDR	-	Wisconsin Epidemiologic Study of Diabetic retinopathy
ETDRS	-	The Early Treatment Diabetic Retinopathy study
VEGF	-	Vascular endothelial growth factor
CSME	-	Clinically significant macular edema
CME	-	Cystoid macular edema
SRD	**-**	Serous retinal detachment
VMT	-	Vitreomacular traction
TPH	-	Taut posterior hyaloids

INTRODUCTION TO OPTICAL COHERENCE TOMOGRAPHY

A variety of imaging modalities have been utilized to assess the retinal pathology. Among the frequently used imaging modalities include the fundus photography, fundus fluorescein angiography, indocyanine green angiography and ultrasonography. However detailed information about the retinal microstructure and quantitative retinal thickness are not obtained by these techniques[1].

Thus there existed a need for a technology which could perform optical biopsy, image at or near the resolution of histopathology without performing an excisional biopsy[2]. Recent advances in fibre optics and technological advancements in laser have provided us with a non contact, high resolution optical biomedical imaging technology called optical coherence tomography[3].

Optical coherence tomography was first invented in 1990 at Massachusetts institute of Technology in boston. First in vivo image of human retina was obtained in 1993 and the first clinical retinal images were obtained in 1995.Optical coherence tomography has become a revolutionary biomedical tissue imaging technique providing a high resolution cross

sectional visualization of retinal structure and other tissues which require micrometer resolution and millimetre depth perception[4].

Low coherence interferometry[5] a classical optical measurement technique along with near broad band light is used by OCT to provide high resolution cross sectional visualization of tissue morphological structure at depth significantly greater than penetrating depth offered by confocal microscopy and conventional bright - field. OCT is analogous to ultrasound imaging, except that it uses light instead of sound.

Presently OCT is being utilized in 3 different fields of optical imaging. First is in macroscopic imaging of structures which can be visualised by the naked eye or with the help of weak magnifications. Secondly is in microscopic imaging using magnifications upto the limit of microscopic resolution. Thirdly in endoscopic imaging, using medium and low magnification[6].

Commercially available optical coherence tomography systems are being used for diverse applications. Few of the areas include in diagnostic medicine notably in ophthalmology where it is being used for obtaining high resolution cross sectional images of anterior segment of the eye and retina. Interventional cardiology is another area where it is being used to help

diagnose coronary artery disease[7]. In combination with catheters and endoscopes enables high-resolution intraluminal imaging of organ systems.

OCT is also being used in non medical fields like in conservation of paintings and in variety of industrial applications like non destructive testing, material thickness measurements and in silicon and semiconductor wafer thickness measurements[8].

OCT offers several advantages over the other imaging techniques

- Non contact and non-invasive.
- Easily tolerated by patients especially the children.
- Changes in macular thickness over time can be assessed.
- Uses safe non ionising radiation.

BASIC PRINCIPLE OF OPTICAL COHERENCE TOMOGRAPHY

OCT is a non contact, non invasive device based on the principle of Michelson interferometry[9]. Broad band with near infrared beam (820nm) coupled to a fiber optic is projected to a beam splitter and reaches the retina and a reference mirror respectively after passing through the ocular media[10]. Boundaries between the retinal microstructures reflect this light and also the light is scattered differently by tissues with different optical properties.

Time delay between light reflected by different layers of retina is compared with time delay of light reflected from reference mirror at a known distance. These reflected pulses from the retina and reference mirror are combined by the interferometer to produce a phenomenon called interference[11].

Photodetector measures the interference. The distance travelled by various light pulses is determined by varying distance to the reference mirror. This produces a range of time delay which is compared. The interferometer constructs a tomogram of retinal structure by integrating several data points over a 2 mm depth which is in real time and represented

using a false colour scale. Degree of light backscattering is represented by different colours.

Thus the OCT image generated has a 10mm axial resolution and 20mm transverse resolution. A scans are aligned using digital processing to correct for eye motion. Signal- to- noise ratio is further improved using digital smoothing techniques[12].

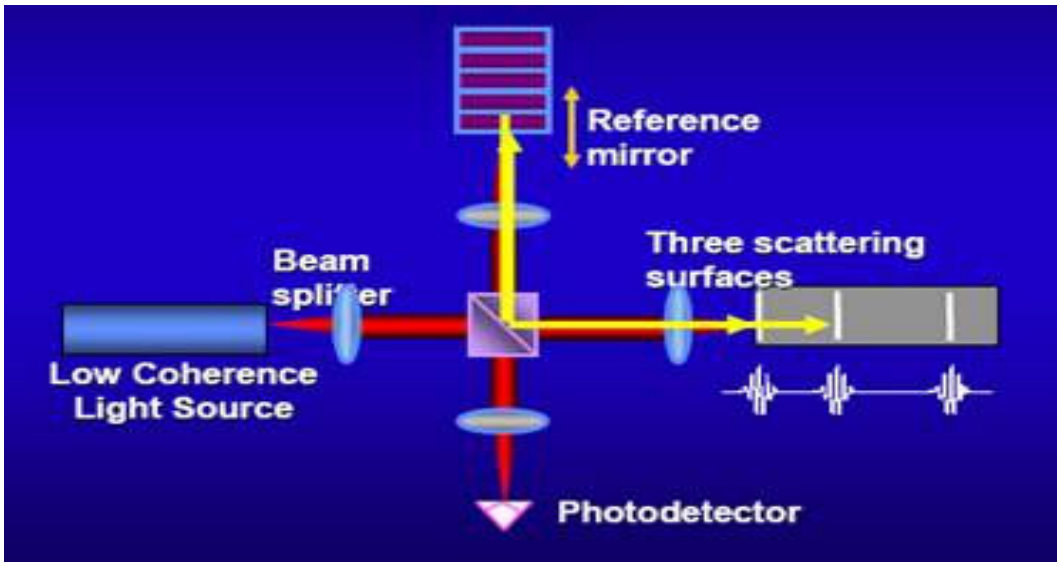
Image display

Retinal image can be acquired by using the OCT even in the absence of pupillary dilation. A 3mm pupil is sufficient for adequate visualization. Retina is focused by adjusting the imaging lens placed at a distance of 1 cm from the eye. Position of the scanning beam over the retina is documented by an infrared- sensitive charge coupled device video camera.

Scan image can be displayed in two forms in an OCT. One is on grey scale where more reflected light appears brighter than less reflected light. Other is using a colour scale where different degrees of reflectivity are represented by different colours. Highly reflective layers appear in bright colours (white and red) and darker colour represents lowly reflective layers (black and blue). Green represents intermediate reflectivity[13].

Fig 1 OPTICAL COHERENCE TOMOGRAPHY

Fig2 PRINCIPLE OF OCT



NORMAL OCT SCAN

OCT allows retina to be studied from vitreous to choriocapillaries and superficial choroidal layers in terms of cross section. Two major structural landmarks seen on a normal horizontal 10 mm scan include the optic disc and fovea.

Optic disc is easily identifiable by its contour on the right side of the tomogram. Optic nerve head cup is seen as a central depression and anterior part of optic nerve is represented by stalk continuing behind the central depression. The characteristic thinning of the retinal nerve fibre layer on the left of the tomogram helps in identifying the fovea.

Dark space anterior to retina represents the vitreous which is not reflective. Vitreo-retinal interface is the interface between non reflective vitreous and the first backscattering retinal layer[14]. The posterior hyaloid is visible as a faint and slightly reflective line which may be in contact with retina or detached.

The retinal nerve fibre layer is thicker on nasal side due to density of papillomacular bundle and is a highly reflective layer. A second hyper-reflective layer is retinal pigment epithelium - choriocapillaries complex which marks the posterior boundary of the retina.

The photoreceptor layer is a minimally reflective layer lying just anterior to RPE -choriocapillaries complex and its poor reflectivity is due to vertical orientation of the photoreceptors[15]. This area is thick in areas of foveal depression. Alternating layers of moderate and low reflectivity lie anterior to layer of photoreceptors representing different layers of neurosensory retina. Plexiform layer are more reflective than nuclear layers. Retinal blood vessels show backscattering.

Different layers of retina have different reflectivity pattern and are represented by different colours in false colour map-

a. Highly reflective layers are the retinal nerve fibre layer and RPE- choriocapillaries complex represented by dark colour.
b. Nuclear layers are hypo-reflective.
c. Plexiform layers are hyper-reflective compared to nuclear layer.
d. Another hyper-reflective structure is the choroid but frequently not well resolved because reflection of light by overlying RPE. Thus the structures oriented vertically in retina have lesser reflectivity and the structures oriented horizontally have higher reflectivity.

INTERPRETATION OF THE OPTICAL COHERENCE TOMOGRAPHY

There are two modes of interpreting an OCT image i.e objective and subjective. Combination of both of these modes is necessary for accurate interpretation of the OCT image[16].

Retinal abnormalities are detected by OCT in terms of thickness, morphology and reflectivity.

OCT must be read in two stages

1. Qualitative and quantitative analysis
2. Deduction and synthesis

The analysis study can be further classified into

QUALITATIVE ANALYSIS

1. Morphological study

Variations in morphology - structural changes in overall retina, retinal outline changes, structural changes within the retina and posterior layers.

2. **Reflectivity study**

Includes shadow areas, hypo-reflectivity and hyper-reflectivity

QUANTITATIVE ANALYSIS

This includes surface mapping, retinal volume and thickness. All the analytical data, results of clinical examination and all the other available data are compared in deductive and synthetic study.

Protocols are available for both qualitative and quantitative estimation in the OCT software.

QUALITATIVE ANALYSIS

several image modification protocols are available for qualitative analysis

1. **Normalize-**

The background noise is eliminated using this protocol and the signal strength is improved. Using this protocol scan images are normalized with respect to noise and signal strength. After application of this protocol to scan images made with different noise or signal strength, the images appear "bright" equally. All of the resulting images have the same range of colour.

2. Align

The errors resulting from movements of the patient in axial direction are corrected using this protocol. Head movement's toward or away from the OCT machine results in vertical shifting of the scan image resulting in low frequency "wiggles". This is corrected by the protocol by comparing

each of longitudinal A- scans in data set with its neighbour. This process is called correlation. Data are aligned by sliding A-scan 1 in relation to A-scan 1 till they align. Then A-scan 3 is aligned with A- scan 2 and this process is repeated till all A scans are aligned thus negating the errors due to the movement of the patients head.

3. Normalize with align

This protocol performs both the above function.

4. Gaussian and median smoothing

These protocols balance the background noise and blend the colours of the scan images. By using these protocols the large scale features in data are better appreciated.

Gaussian smoothing calculates a moving average of signal values in 3x3 regions. Gaussian function is used to weigh the signal values. The outer points are weighed less compared to the centre point and there by average are calculated.

Similar to Gaussian smoothing is the median smoothing. Difference being the median smoothing utilizes the median value of the 3x3 region unlike the gaussian smoothing which uses the moving average. Median smoothing has the advantage of preserving small details in data which are lost in Gaussian smoothing.

5. **Proportional**

This protocol provides an image that is true in its horizontal and vertical proportions. Usually the scan image is elongated vertically allowing complete visualization of longitudinal plane. After using this protocol the image produced is compressed vertically.

6. Scan profile

The signal values for all data points are provided by this protocol. The graph changes dynamically on moving the cursor over the OCT image. These image processing protocols can be used prior to objective assessment of the OCT scan image. These protocols apply mathematical algorithms for giving the visual analysis .

MORPHOLOGICAL STUDY

Deformation of retina

A) Concavity:

In certain conditions the OCT may show the presence of pronounced concavity as in posterior staphyloma and high myopia. However processing the scan image using the alignment function may make the concavity less pronounced.

B) Convexity:

Sub retinal cysts and retinal pigment epithelial detachment produce convexity which can be accurately detected by performing on OCT imaging.

DEFORMATION OF THR RETINAL PROFILE

a. **Disappearance of foveal depression**

   Foveal depression can be lost in retinal condition such as macular edema sub-foveal retinal detachment and other pathologies. This alteration n foveal contour can be accurately identified by OCT imaging technique. Assessing the foveal contour also helps in predicting the response to the treatment.

b. **Epiretinal membrane**

   Can have various presentations, either adherent or separate from the retina. Folds may be visible on the retinal surface.

c. **Macular pseudo hole or lamellar macular hole**

d. **Macular holes**

   OCT plays a important role in diagnosing and staging of macular hole. Diameter and extent of the detachment can be assessed by using OCT

INTRARETINAL STRUCTURAL CHANGES

a. Cysts in cystoid macular edema appear as hypo reflective spaces of varying size. These are mainly confined to the outer retinal layers. Fusion of these spaces can occur in chronic cases leading to formation of very large cystic spaces occupying the full thickness of retinal layers.
b. Pseudoholes
c. Hard exudates are hyper-reflective shadows at the margin of the edematous and normal retina and block the reflections from the underlying retina.
d. Cotton wool spots are hyper-reflective retinal nodules in nerve fibre layer are present at margins of ischemic lesions of NFL.

POSTERIOR MORPHOLOGICAL CHANGES

a. Retinal pigment epithelial detachment produce deformation of posterior retina on OCT scan. These form a steep angle with the choriocapillaries.
b. Serous retinal detachment of form shallow angles with RPE
c. Drusens are seen as irregularities and wavy undulation of the RPE and choriocapillaries.

d. Choroidal neovascular membrane appears as nodular rounded fusiform structures anterior to RPE. Edema and serous retinal detachment may be present. Occult neovascular membranes are difficult to detect.

REFLECTIVE STUDY

An OCT scan may show areas of increased or decreased reflectivity or shadow areas whenever retinal pathology is present.

Shadow areas

A OCT scan shows a shadow area when a area of dense, hyper-reflective tissue is present producing a screen which may be complete or incomplete. Elements lying behind the shadow area are concealed.

Anterior shadow and screen effects are seen in

Normal - Retinal blood vessels

Abnormal - Hemorrhage

- Exudates

Posterior shadow and screen effects are seen in

- Pigment epithelial hypertrophy/hyperplasia
- Accumulation of pigment
- Retinal scars
- Choroidal nevi

QUANTITATIVE ANALYSIS

a) Retinal thickness/ volume

Thickness and volume of the retina are obtained by using this protocol in the form of two circular maps one for each eye.

b) Retinal thickness/volume tabular

This protocol in addition to providing retinal thickness and volume also provides a table that displaying average thickness and volume of retina in each quadrant, ratios and differences between the quadrants and between the 2 eyes.

c) Retinal thickness/volume change

Retina thickness /volume changes in between examinations can be assessed using this protocol.

OCT SCAN PROTOCOLS

various scan acquisition protocols are offered but the Stratus OCT 3. Appropriate protocols have to be used to get most accurate information.

OCT SCAN PROTOCOLS FOR IMAGING MACULA

1. Line scan
2. Radial scan
3. Macular thickness map
4. Fast macular thickness map
5. Raster lines
6. Repeat scan

ANALYSIS PROTOCOLS

1. Retinal thickness
2. Retinal map
3. Retinal thickness/volume

Line scan

Using this protocol multiple line scans can be acquired without the need of returning to the main window. Default angle being 0^0. Nasal position is taken as 0^0. It is possible to alter the length and angle of the line scan with 5 mm being the default length of line scan. Resolution of scan

image is inversely proportional to the length of the line scan. Protocol also helps in acquiring multiple scans of different parameters .

Radial scan

This protocol is a combination of 6 to 24 line scan which pass through a central common axis and are equally spaced. Size and parameters can be varied .Default setting consists of 6 lines each of which measure 6 mm in length. By adjusting the size of the aiming circle the length of these line scans is altered. However this change has to be made before saving the first scan. Macular scan and retinal thickness/volume analysis can be acquired using radial scans.

Macular thickness map

Similar to radial lines with only difference being that the aiming circle has a fixed diameter of 6mm.useful for retinal thickness measurement.

Fast macular thickness map

This protocol acquires 6 scans each of 6 mm length quickly i.e within 1.92 second .It is not possible to alter the size and number of scans in this protocol. This protocol is used with retinal thickness analysis and by performing in both the eyes retinal thickness and volume can be compared between the two eyes.

Raster lines

Using this protocol about 6 -24 line scans are obtained which are parallel and spaced equally. These line scans are acquired over a rectangular area. Size of this area can be altered to include the entire area of pathology. This protocol is useful when one wishes to acquire scan at multiple levels as in choroidal neovascular membrane. Default area is a 3mm square consisting of 6 lines which are acquired from superior to inferior followed by nasal to temporal.

Repeat

Using this protocol it is possible to repeat any of the previously saved protocols which utilize the same parameters like size, angle, placement of fixation and landmark. It is not possible to change any of the parameters except for the placement. Landmark is placed on reference point helping in reproducibility during repeat scan. Landmark can be placed accurately by looking at the previous image which can be displayed on the screen.

OCT AND SCANNING LASER OPHTALMOSCOPE TECHNOLOGY

Two specific limitations of OCT include

1. Errors in A - scan image correlation and interpolation- The image quality becomes less reliable due to increase in correlation and interpolation errors of A-scan as the scan length increase from 3 to 10 mm.

2. Precise anatomic localization of the OCT image from the red free image - The red free image showing the position of OCT is not pixel linked. Because of this the precise anatomic localization is compromised. A newer device is being developed which provides precise OCT image localization. It creates OCT B- scan image and uses simultaneous red free scanning laser ophthalmoscope to achieve this. Horizontal scanning is performed in ophthalmoscopic plane at increasing depths to create OCT B -scan images. C scan image is produced by accumulating information from entire plane of tissue at varying depths. 3-D OCT images can be constructed by processing numerous C scan images allowing for linear and volumetric measurements.

This device utilizes a beam splitter at the light source to produce two channels. Conventional SLO is used by one channel to produce red free image by one channel. Other channel is used to produce simultaneous OCT images and precise anatomic localization is possible since these images are pixel linked. Hence this device provides better resolution and image localization than conventional OCT.

RECENT TECHNOLOGICAL ADVANCEMENTS IN OCT TECHNOLOGY

a) ULTRA HIGH RESOLUTION OCT

A recent improvement in OCT technology is ultra high resolution OCT[17] that allows for unprecedented in vivo sub cellular and intraretinal visualization. UHR OCT provides a superior axial image resolution of compared to that of conventional OCT and thus allows enhanced visualization of retinal layers and can perform a non invasive biopsy of retina[18].

This improvement is achieved by using ultra broad bandwidth light source instead of super luminescent diodes used in conventional OCT. A clinically viable UHR OCT based on femtoseconds titanium-sapphire laser was developed by Drexler and Fujimoto.

UH OCT is an time domain OCT which provides a axial resolution of 3 microns and transverse resolution of 15- 20 microns and provides with both A scan and B scan imaging capabilities. It utilizes femtoseconds sapphire laser which provides a light with 815 nm wavelength and 125 nm bandwidth allowing for visualization of foveal and optic disc contour and internal architecture of retina and choroid which the conventional OCT would not be able to resolve.

b) 3D – OPTICAL COHERENCE TOMOGRAPHY

Is the latest technological advancement in the field of OCT which uses higher speeds and acquires more data in less time providing unparalleled view of the retinal and subretinal structures with best resolution. 3D-OCT is base on principle of spectral domain technology[19]. Conventional OCT and UHR OCT are based on time domain principle. The moving parts in conventional OCT are replaced by a stationary spectrometer in SD-OCT.

Conventional OCT are depend on mechanical movements of internal components to measure retinal thickness hence limiting the speed and number of scan acquisitions. Current time domain OCT instruments measure on 5% of the macular area and approximate 95% of the output data. Hence a chance to miss very small focal lesions but SD-OCT captures a grid of data in macular area and is unlikely to miss these small focal lesions. 3D-OCT uses super luminescent diode laser which produces light of 840 nm and 50 nm bandwidth. It provides axial resolution of 5 microns and transverse resolution of <20 microns. 3D-OCT can capture 256 B-scans in succession providing a 3 dimensional cube of details which can be viewed as C- scan.

COMPARISON OF OCT WITH STANDARD TECHNIQUES OF RETINAL IMAGING

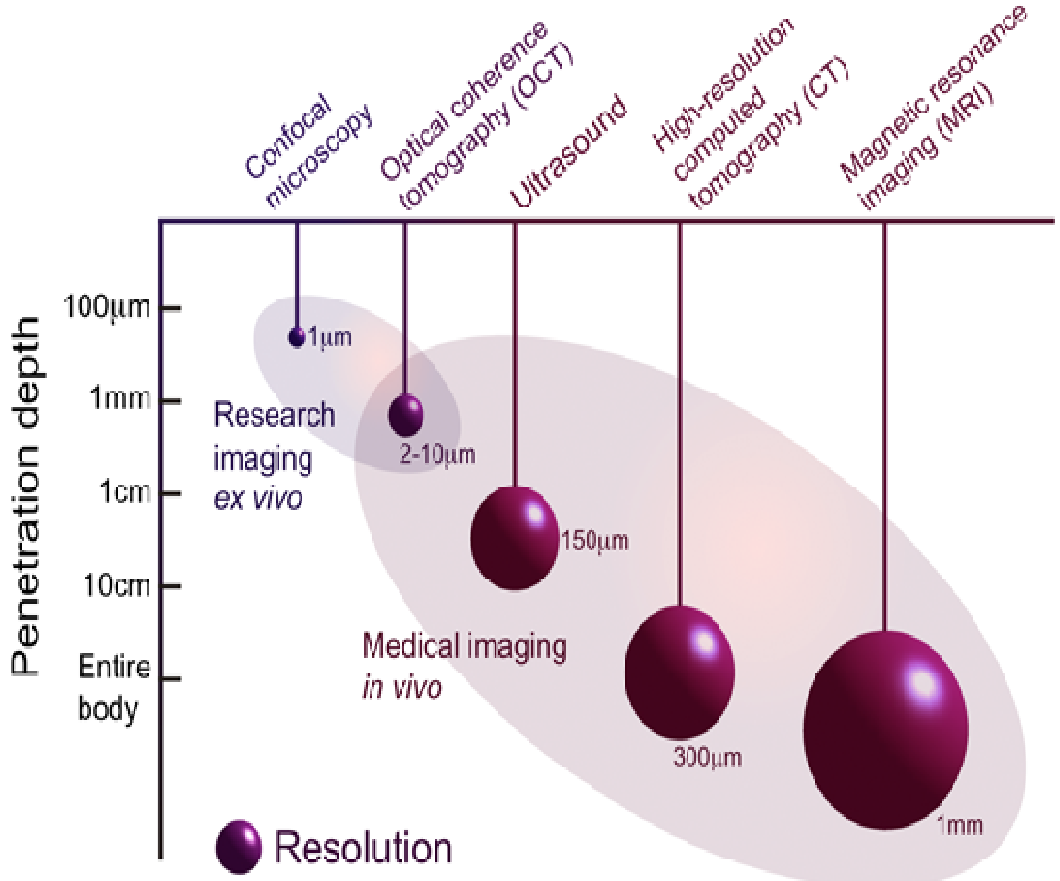
Macular thickness can be evaluated by other technique like stereo-fundus photographs and fluorescein angiography. Retinal thickness assessed by stereo - fundus photography and macular hyperfluorescence on FFA correlates well with retinal thickness measured by OCT.

However macular hyperfluorescence on FFA may not always show increased thickness on OCT and vice versa. Quantitative assessment of retinal thickness and cross sectional retinal morphology cannot be assessed by fundus photography and FFA. But origin of macular fluid and retinal microvascular abnormalities are well defined by FFA and subtle macular lesions are demonstrated by fundus photography which is not provided by OCT[20]. Thus all three imaging techniques provide complementary information regarding macula.

COMPARISON OF OCT WITH OTHER IMAGING MODALITIES

Different criteria can be used to compare OCT with other imaging modalities which include depth of imaging, resolution, acquisition time, complexity and intrusiveness. Imaging depth of OCT is limited to few millimetres less than CT, MRI or ultrasound but has greater resolution compared to these modalities.

However confocal microscopy is better than OCT in all these aspects. The acquisition time in OCT is short similar to the ultrasound sufficient to support topographic imaging and is thus more tolerant to subject motion than CT OR MRI.OCT doesn't require contact with and can be used in air filled organs like the ultrasound.



COMPARISON OF OCT WITH CONFOCAL MICROSCOPY, CT, MRI AND ULTRASOUND

INTRODUCTION

About 4 percent of world population are estimated to be affected by diabetes mellitus almost half of who have some degree of diabetic retinopathy at any given time[21]. In about 86% of type 1 and 33% of type 2 DM patients in western population suffered visual loss due to diabetic retinopathy[22].

World health organisation reported that there has been an epidemic increase in type 2 DM in India .More than 90% of the patients have type 2 DM being diagnosed usually in 4th decade. However the prevalence of type 2 DM is increasing in children and adolescent population.Diabetic retinopathy is becoming a important cause of visual disability.

One of the leading causes of blindness worldwide is diabetic retinopathy. (wilkinson 1988). It is preventable. DR is basically a microangiopathy occurring as a complication of both the types of diabetes. Main structures which are affected in this condition are the precapillary arterioles, capillaries and venules capillaries and venules.

Thus diabetic retinopathy is a microangiopathy

In a population based study, Chennai Urban Rural Epidemiology (CURES) [23]Eye Study, in which representative sample of 26,001 individuals (urban Component) were included, 17.6% of 1715 diabetic patients were found to have diabetic retinopathy. This study used stereo retinal photographs and Early Treatment Diabetic Retinopathy Study (ETDRS) grading to document DR in the Indian population[13].

ANATOMY OF THE HUMAN RETINA

Retina is the only part of central nervous system which can be visualized noninvasively as a thin delicate transparent membrane.

Retina can be divided into 3 parts

1) Optic disc

1.5 mm well defined circular area appearing pale pink in colour. It is located about 3 to 4 mm nasal to the fovea. This site of optic disc sees the termination of all the layers of retina except the nerve fibre layer. This layer passes through the disc forming the optic nerve. Optic disc has a central depression called physiological cup which is the entry site for retinal blood vessels. It represents the physiological blind spot .Blind spot is not perceived when both the eyes are open because of overlapping of the visual feilds of both eyes. About 1 to 1.2 million neurons exit from the eye towards the brain.

2) Macula lutea

Macula lutea meaning yellow spot in latin is a 5.5mm dark area situated at the posterior pole. Yellow colour of macula is due to the presence of lutein and zeaxanthin which are the yellow xanthophyll carotenoids. It has an elliptical configuration and is located between the upper and lower arcuate vessels and temporal retinal vessels.

Macula can be further divided into

a) Fovea centralis

It is the central depressed region of the macula. It is about 1.85 mm in measurement.

b) Foveola

It measures 0.35mm from central floor of fovea and is located 2 disc diameter from temporal edge of the disc and 1dd below the horizontal meridian. It has the highest density of cones (1, 99,000/mm^2) which are narrower and elongated for maximum detection of light. Foveola contains only cones and few muller cells.

c) Umbo

It appears as a tiny dip at the centre of foveola. It forms the foveolar reflex which is lost in early stages of macular pathology.

d) Foveal avascular zone[24]

It is present within the fovea but outside foveola and measures 1.5mm. In this area there are no retinal capillaries and hence fovea is dependent solely on choriocapillaries for blood supply in this region.

e) Parafoveal and perifoveal regions

These regions lie 0.5 and 1.5 mm around the fovea.

3) Peripheral retina

Includes the remaining parts of the retina outside the temporal retinal arteries. Anatomically this region of retina has only one layer of ganglion cell. It is further divided into

a) Near periphery	-	Area of 1.5mm around the macula
b) Mid periphery	-	Area of 3mm around near periphery
c) Far periphery	-	Extends 16mm from optic disc on nasal side and 10mm on temporal side in horizontal meridian

d) Ora serrata - is the region where retina ends and pars plana of ciliary body starts. Its width is about 2.1mm temporally and 0.7 mm nasally. It distance from limbus is 6mm nasally and 7 mm temporally is 6-8mm.

Fig 3 OPTIC DISC

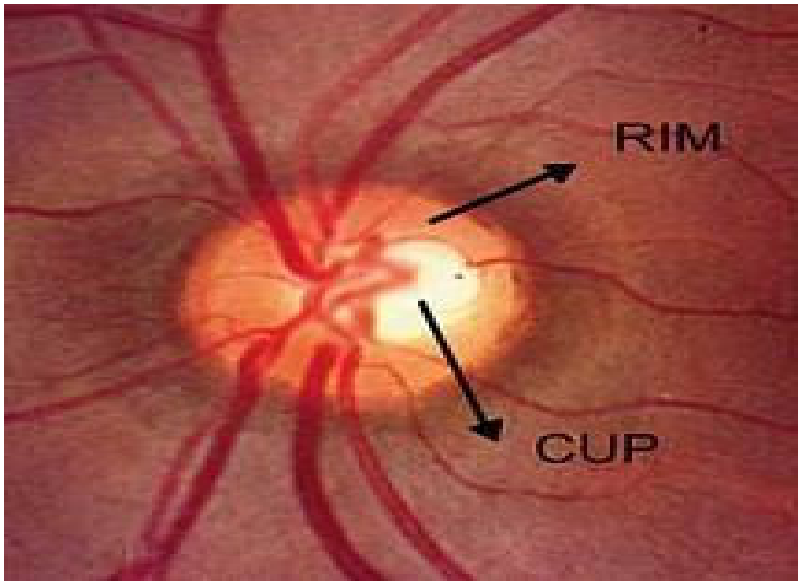
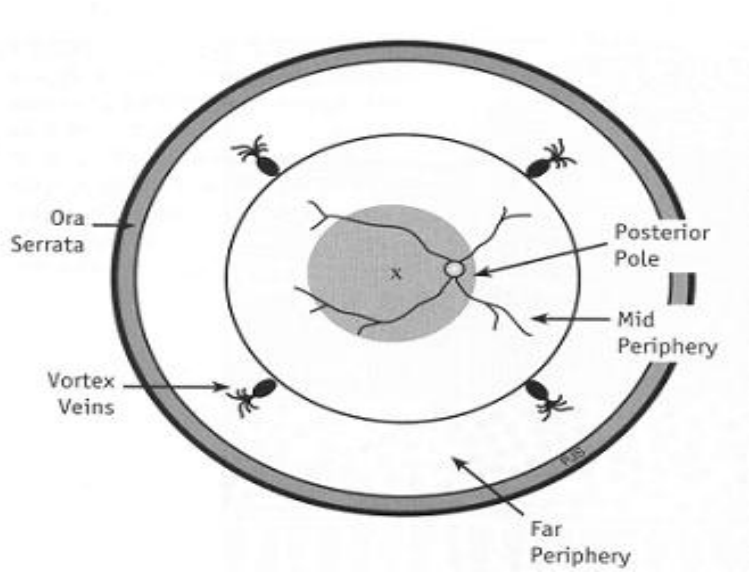


Fig 4 MACULA AND PERIPHERAL RETINA



HISTOLOGY

10 layers have been described in retina. From posterior to anterior include

1. Retinal pigment epithelium

Made up of a single layer of hexagonal cells which contain pigment granules. This layer is firmly adherent to underlying bruch's membrane and loosely attached to overlying photoreceptors. Sub retinal space is the potential space between RPE and photoreceptor layer.

2. Photoreceptor layer

This layer consists of end organs of vision i.e photoreceptors (rods and cones).There are about 120 million rods and 7 million cones. Rods re absent in fovea.

3. External limiting membrane

It is a fenestrated membrane formed by the junctions between cell membrane of photoreceptors and muller cells. It is not a true basement membrane. Processes of photoreceptors pass though these fenestrations.

4. Outer nuclear layer

This layer is formed by the nuclei of photoreceptors i.e rods and cones. The number of rows of nuclei and thickness of this layer varies in different region of retina.

5. Outer plexiform layer

It is made up of synapses between the rod spherules and cone pedicles with the dendrites of bipolar cells and processes of horizontal cells.

6. Inner nuclear layer

This layer consists primarily of nuclei of bipolar cells. This layer is absent in fovea.

7. Inner plexiform layer

Consists of synapses between the axons of first order neurons (bipolar cells) with dendrites of second order neurons (ganglion cells)

8. Ganglionic cell layer

This layer is made up of bodies and nuclei of ganglion cells. Most of the retina has a single layer of ganglion cells, it is multilayered in macular region .It has 2 layers on temporal side of the disc.

9. Nerve fibre layer

This layer is composed of unmyelinated axons of ganglion cells. These axons converge at optic disc and after passing through the lamina cribosa become myelinated.

10. Internal limiting membrane

It is the innermost layer. It forms the interface between the retina and vitreous.

BLOOD SUPPLY OF RETINA

Retina has a dual circulation. Outer retinal layers are avascular and they depend on adjacent choroid for nutrition. Choroidal circulation is supplied by the ophthalmic artery. Choriocapillaries supply the outer one third of retina and the inner two thirds are supplied by central retinal artery which is also a branch of the ophthalmic artery.

In the presence of cilioretinal artery the choroid also supplies the inner retina.

The retinal arteries are end arteries. These arteries run outwards within the nerve fibre layer towards peripheral retina. The smaller arterioles form 2 types of capillary systems. One is horizontal which supplies the nerve fibre layer .Second are the deeper branches which run into retina to forming one peripheral and perifoveal network and 4 peripapillary network. Thus all the layers of neurosensory retina are supplied by the retinal circulation except the layer of photoreceptor which is supplied by the choroid.

There are two capillary free zones one around arterioles and at the fovea which is supplied by diffusion from the choriocapillaries. All the capillary blood runs back to central retinal vein which ends by draining into ophthalmic vein or into cavernous sinus directly.

Elastic tissue and smooth muscles are absent in retinal capillary wall which comprises of

1. Endothelial cells forming a single layer on basement membrane. Tight junction links the adjacent endothelial cells.
2. Pericytes with multiple pseudopodial processes envelop the capillaries and lie external to endothelial cells. These pericytes play a role in auto regulation of micro vascular circulation.

BLOOD RETINAL BARRIER

Retina has two blood retinal barriers - outer and inner blood retinal barrier. Tight junctions between the endothelial cells of retinal capillaries form the inner BRB which surrounds all the retinal blood vessels where as the zona occludens between the RPE form the outer blood retinal barrier. Both these control the retinal microenvironment. Lipophillic molecules and very small molecules like oxygen can pass through these barriers.

EPIDEMIOLOGY

The Wisconsin Epidemiologic Study of Diabetic retinopathy (WESDR) [25]documented prevalence of macular edema in 11% overall among patients with diabetes in sothern wisconsin[n]. Prevalence was higher in early onset compared to patients with older onset diabetes. Strong association was noticed with duration and glycemic status

In some diabetic populations the retinopathy prevalence including that of DME and CSME appears to be declining due to improved glycemic control of diabetes.

However the overall prevalence of DME is increasing due to increasing prevalence of diabetes in industrialized nations .

The WESDR determined a 10 yr rate of DME of 20% in young onset diabetic patient, 25.4% in older onset diabetics on insulin and 13.9% in older onset group not on insulin. 99% of type 1 and 60% of type 2 DM pts develop DR after 20 yrs.

3% of patients with mild NPDR, 38% of patients with moderate to severe NPDR have DME. 71% of patients with PDR also develop DME.

RISK FACTORS AND CLINICAL ASSOCIATIONS

1) Severity

Severity of DR has a strong and positive correlation with macular edema. Since most patients with PDR do not have DME and vice versa, ETDRS[26] described DR severity scale based on progression to high risk PDR and excluded retinal thickness per se as a additional risk factor.

2) Duration

Most important risk factor. About 50% of the patients diagnosed with diabetes before 30 years develop retinopathy after 10 yrs which increases to 90% after 30yrs. 5% of type 2 DM patients have retinopathy at presentation. Duration of DM also has a strong relationship with prevalence and incidence of macular edema

3) Poor glycemic controls.

Second most important risk factor indentified for DME is glycemic control. Intensive control of glycemic status has shown to reduce the progression of DR, nephropathy and neuropathy as shown by the Epidemiology of Diabetes Intervention and control study.

4) Pregnancy

Rapid progression of retinopathy may be seen in pregnancy[27] and the risk is dependent on severity of DR in 1st trimester. DME has been seen to

worsen in pregnancy and is often associated with preexisting retinopathy and preeclampsia. Poor glycemic control in pregnancy is also a contributing factor.

5) Hypertension

United Kingdom prospective diabetic study (UKPDS) suggested that visual loss from macular edema can be ameliorated by having a strict control of systemic hypertension in type 2 DM[28].

6) Nephropathy and proteinuria

Proteinuria is positively correlated with DR however the relationship between renal failure and macular edema has not been clearly established. Studies have demonstrated an increase in macular edema occurring in patients who had fluid retention which improved following diuretics or hemodialysis.

7) Dyslipidemia

It is an independent risk factor for DME[29].

8) Intraocular surgery

May worsen the existing DME. Worsening of DME has been observed in patients who had coexisting cataract and DME and underwent cataract surgery before managing DME[30].

9) Intraocular inflammation

10) Panretinal photocoagulation , Laser for PDR

Worsening of DME has been observed in patients following PRP before managing the macular edema. ETDRS research group suggested performing management of macular edema before doing a PRP in PDR patients with DME.

11) Anemia

Hypoxia resulting due to anaemia leads to development of microaneurysms and also leads to other changes in retina.

12) Association with genes

People with HLA DR4 and DR5 phenotype have been found to be having increased risk of developing PDR

13) Protective ocular factors

Patients with glaucoma and high myopia have been found to be having lesser prevalence of DR. Also the severity of DR is reduced in these patients. This has been attributed to lower metabolic demands of the retina in these patients.

PATHOPHYSIOLOGY

Diabetic retinopathy changes occur as result of combination of several factors which can be structural, rheological, and biochemical.

1) Structural changes associated with diabetic retinopathy

As the blood glucose level increases the tight junctions between the endothelial cells of capillaries breaks down. There is an increase in transcellular endocytosis resulting in fluid movement into retinal tissue from the vessel wall.

At some stage the fluid reuptake mechanism of retina is overwhelmed by this fluid accumulation resulting in retinal edema

There also occurs

1. Thickening of capillary basement membrane
2. Pericyte loss
3. Endothelial cell loss
4. Dysfunction of endothelial cell

2) Rheological changes

1. **Abnormalities of platelet function** - Platelets become abnormally adhesive and aggregate more. Also the survival of platelets is reduced
2. **Abnormalities of red blood cell function** - Which include reduced deformability and increased rouleaux formation.

3. **Blood Protein abnormality -** Fibrinogen, haptoglobulin, alfa 2 macroglobulin levels in blood are increased.

3) Biological changes

1) Long standing hyperglycemia.

Advanced glycation end products are formed due to non enzymatic binding of sugars to proteins. These end products play a crucial role in producing diabetic complications.

2) Sorbitol pathway

Aldose reductase is an enzyme which converts glucose to sorbitol. Sorbitol dehydrogenase converts the sorbitol to fructose. However the reaction catalyzed by sorbitol dehydrogense is slower leading to building up of toxic levels of sorbitol which cause endothelial damage.

3) Vascular endothelial growth factor.

Has been detected in diabetic retinas, It increases vascular permeability leading to DME.

4) Protein kinase c - is emerging as another target molecule for pharmacological management of DME. It is selectively up regulated by hyperglycemia and has been found to play a role in pathogenesis of DME.

CLINICAL PRESENTATION

Depending on the degree of involvement of fovea the symptoms experienced by the patients with DME vary widely. Gradual painless progressive loss of vision, colour vision loss, defective night vision and dark adaptation is experienced by the patient

DME shows following features on clinical examination

a. Macular thickening
b. underlying pattern of choroidal vessels gets blurred
c. Absent foveolar reflex following involvement of fovea
d. Formation of intraretinal cystic spaces.
e. Hard exudates which are lipoproteinaceous materials which may be arranged in a ring like pattern called circinate retinopathy.

CLASSIFICATION OF DIABETIC MACULAR EDEMA.

There are classified as

a) Focal type of macular edema

This type of macular edema is characterized by presence of focal areas of leakage due to presence of microaneursyms and capillary segments which are dilated. Adjacent normal retina is separated from these areas by hard exudates which may be arranged in the form of complete or incomplete rings.

b) Diffuse type of macular edema

It is characterized by breakdown of the blood retinal barrier. There is leakage from Microaneurysm and dilated capillary bed throughout the posterior pole. It can have a bilaterally symmetrical presentation. Exacerbation and amelioration of diffuse macular edema is noted in association with systemic factors like renal, cardiovascular, systemic hypertension.

C) Ischemic

Has a variable presentation and may have a normal looking macula with low visual acuity. FFA shows enlargement of FAZ with foveal non perfusion and other capillary drop out areas in posterior pole and periphery.

d) Mixed type - Combination of any of the above type.

CLINICALLY SIGNIFICANT MACULAR EDEMA AS DEFINED BY ETDRS

ETDRS[31] defined clinically significant macular edema (CSME) as

- Retinal thickening within 500mm of centre of the macula.
- Exudates within 500 mm of centre of macula , if associated with retinal thickening (which may be outside 500mm)
- Retinal thickening of one disc diameter or larger any part of which is within one disc diameter of centre of the macula

INTERNATIONAL CLINICAL DIABETIC MACULAR EDEMA SEVERITY SCALE classified DME as

a) Diabetic macular edema absent - Absence of any retinal thickening or hard exudates in posterior pole

B) Diabetic macular edema present - Retinal thickening or hard exudates of some degree in posterior pole.

C) Mild diabetic macular edema - Presence of retinal thickening or hard exudates in posterior pole but distant from centre of macula.

D) Moderate diabetic macular edema - Retinal thickening or hard exudates approaching centre of macula but not involving it.

E) Severe diabetic macular edema - Hard exudates or retinal thickening involving centre of macula

Fig 4 FOCAL MACULOPATHY WITH FOCAL LEAK PATTERN

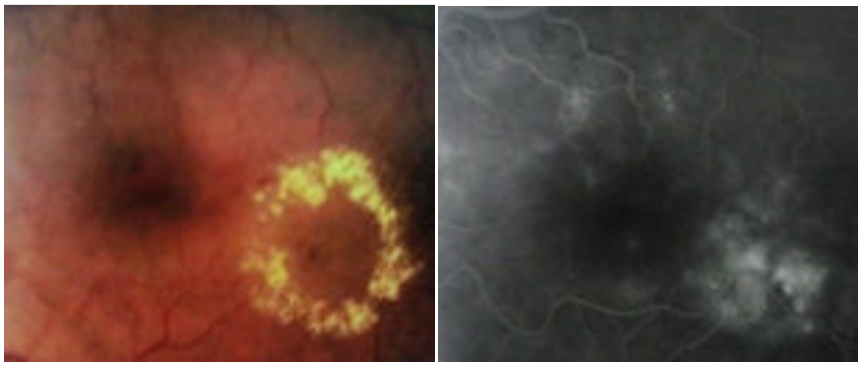


Fig 5 DIFFUSE MACULOPATHY WITH DIFFUSE LEAKAGE

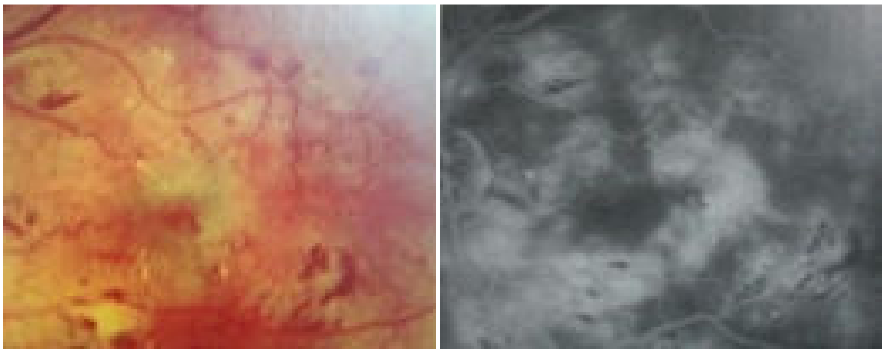
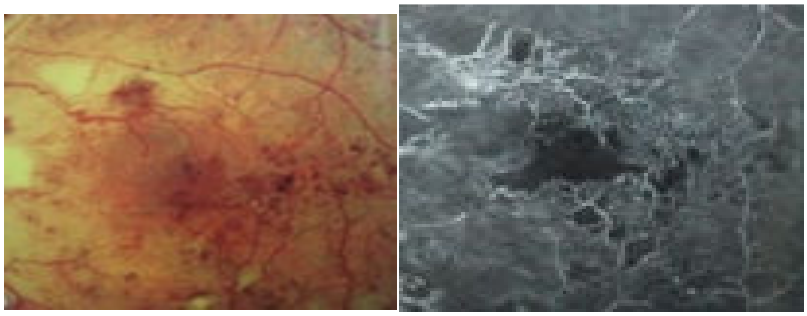


Fig 6 ISCHEMIC MACULOPATHY WITH ENLARGED FAZ



CLINICALLY SIGNIFICANT MACULAR EDEMA (Fig 7,8,9)

Fig 7

Fig 8

Fig 9

EVALUATION OF PATIENTS WITH CSME

various parameters assessed in examination include

1) Visual acuity

Commonly assessed with the snellens distance vision chart or log mar chart.

2) Colour vision

Tests used is Fransworth Munsell 100 hue test. In patients with DME the sensitivity of blue cones is reduced. Most common defect observed is blue yellow.

3) Fields

Charting of fields by tangent screen shows the presence of scotomas. These scotomas correspond to the retinal area of involvement.

4) Slit lamp biomicroscopy

Allows the assessment of anterior segment pathology and cataract and when combined with 90 / 78 D lens provides a stereoscopic view of the fundus which is very useful in cases of CSME.

5) Direct ophthalmoscophy

Provides higher magnification but limited field of view for examination.

6) Indirect ophthalmoscopy

Provides a wider field of view but lesser magnification. Useful for examination of the periphery and in media opacities.

7) Amsler grid

Allows for assessment of patients central visual field

8) Electrophysiological tests

a) Electroretinography - Macular edema is associated with abnormalities in ERG like delay in implicit time and abnormalities of oscillatory potential in ascending limb of b wave.

b) Electrooculography - shows abnormal Ardens Ardens ratio

c) Visually evoked potential - shows amplitude reduction .latency remains normal.

9) Fundus fluorescein angiography

Plays a role in diagnosing, documenting, determining the pattern of leak, deciding on mode of treatment and follow up of treated patients.

10) Optical coherence tomography

Helps to determine the pattern of DME, retinal thickness, management option and follow up.

OPTICAL COHERENCE TOMOGRAPHY IN DIABETIC MACULAR EDEMA

Diabetic macular edema produces several changes at ultra structural levels of the retina. Topographic view obtained with two dimensional imaging techniques like fundus photography and FFA help in delineating the treatable lesions but do not provide an insight into the changes occurring within retinal layers which is provided by OCT.

The main purpose of doing an OCT in clinically significant DME are

- Define the pattern of DME
- Post treatment follow up of anatomical changes
- Define indications for vitrectomy.

Though slit lamp examination is very sensitive for detecting CSME qualitatively and FFA for the type of fluid leakage, qualitative assessment and quantitative measurement of retinal thickness correlates better with retinal dysfunction in patients of CSME as shown by numerous studies.OCT allows the study of subclinical retinal changes that may not be detected by FFA and slit lamp bio microscopy.

5 patterns of structural changes have been described in CSME in OCT.

1) Sponge like retinal thickening

Appears as thickening of retina without definite cystic spaces. It is mostly confined to outer retinal layers as the intraretinal fluid accumulation caused backscattering. Hard exudates appear as areas of hyper-reflectivity within the retinal layers with backscattering.

2) Cystoid macular edema

OCT imaging reveals the presence of several hypo-reflective cystoid spaces with intervening septa located mainly in the outer retina. Size of the cysts may vary. In long standing cases large cysts are formed due to fusion of multiple smaller cysts.

3) Serous retinal detachment

Horizontal scan through fovea in these cases show an area of hypo reflectivity in sub retinal layers corresponding to areas of detachment due to accumulation of fluid. These areas may disappear spontaneously following laser.

4) Taut posterior hyaloids

OCT imaging in these cases shows the presence of taut posterior hyaloid as a hyper reflective membrane. Bio microscopic examination may reveal taut, shiny, glistening membrane associated with retinal striae. It may cause recalcitrant macular edema[n].

5) Vitreomacular traction

This can result in detachment of the fovea. Laser can worsen the macular edema in such eyes and are subjects for vitrectomy to release the traction.

Both VMT and Taut posterior hyaloid may be causes of recalcitrant macular edema with foveal detachment. Both of these conditions can be diagnosed easily on OCT, even when they are subclinical. Pars plana vitrectomy is indicated in both the conditions.

Fig 10 SPONGY PATTERN OF CSME

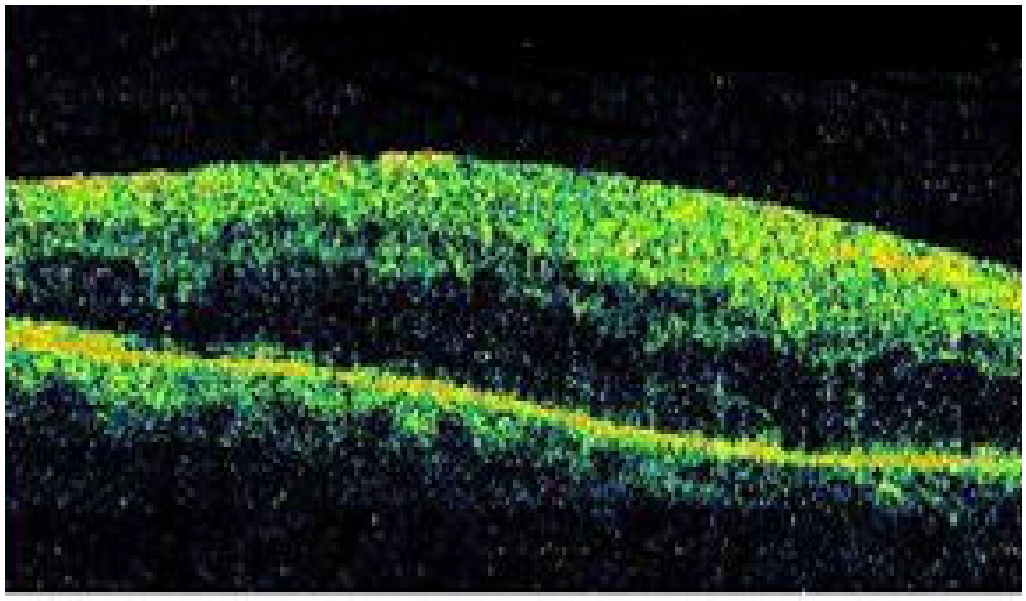


Fig 11 CYSTOID MACULAR EDEMA

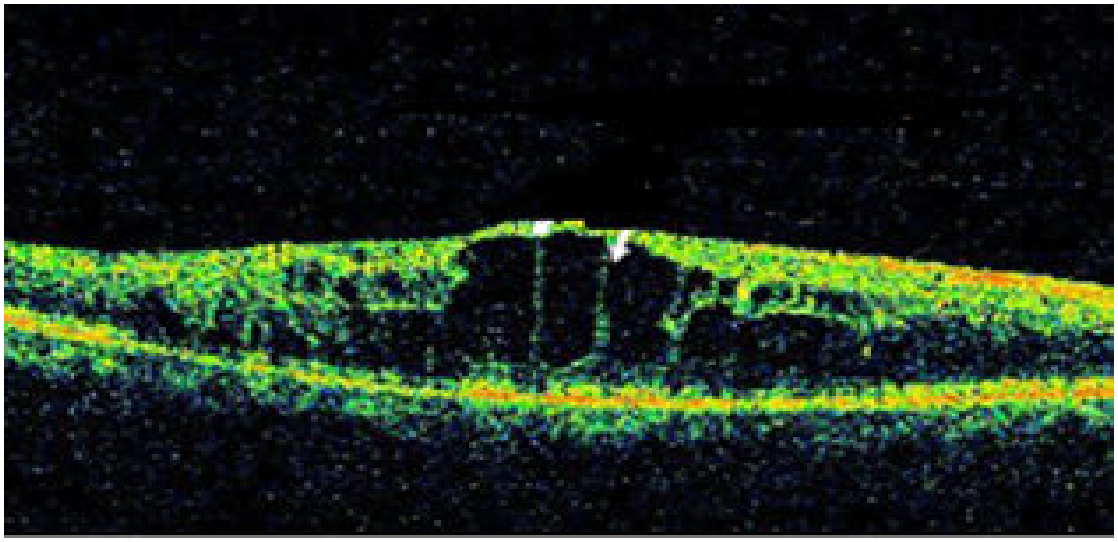


Fig12 SEROUS RETINAL DETACHMENT

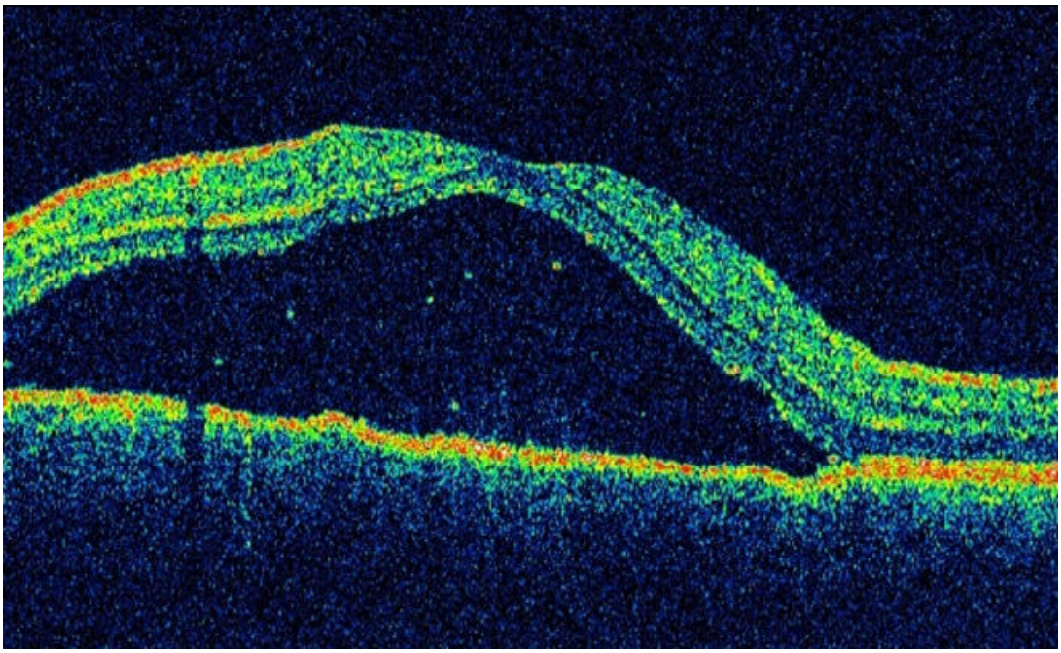


Fig 13 TAUT POSTERIOR HYALOID

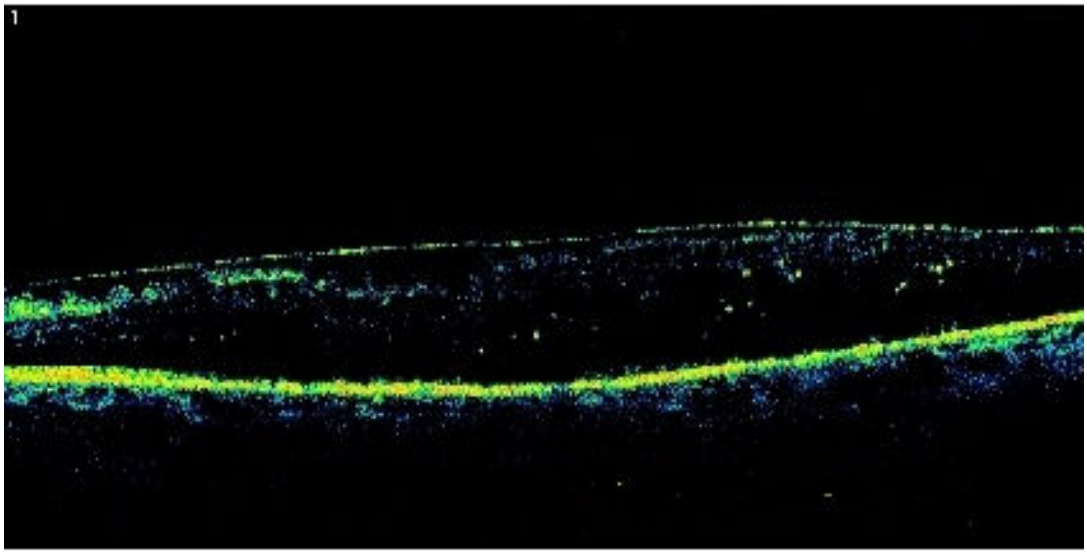
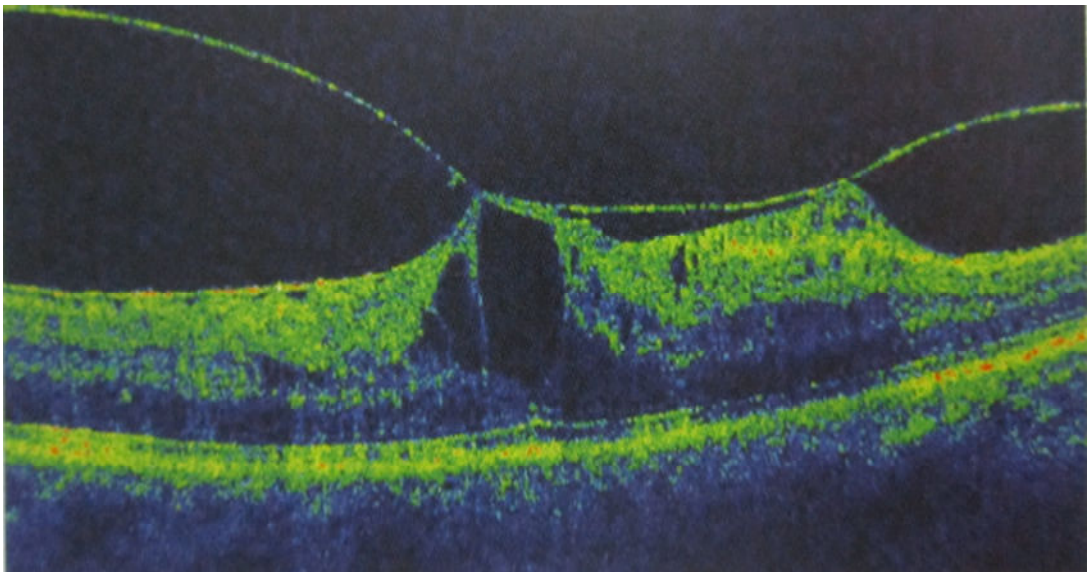


Fig 14 VITEROMACULAR TEACTION



BREIF OVERVIEW OF MANAGEMENT OF CSME PREVENTION AND CONTROL

Incidence and progression of DR can be reduced by having optical metabolic control as shown by the Diabetes Control and Complication Trial(DCCT) and the united kingdom prospective diabetes study(UKPDS)[32]. A reduction of macular edema was noticed even before laser therapy by strict control of risk factors like HbA1c, blood pressure, anemia, lipid profile and proteinuria. Suggested Cut off value for blood pressure, LDL cholesterol and HbA1c are <130/80, <100mg/dl and <7% respectively.

LASER TREATMENT FOR CSME

The ETDRS study demonstrated that laser treatment reduced the risk of moderate visual loss (loss of 3 or more lines in snellens equivalent / 15 or more letters on ETDRS chart) and improved the chances of visual improvement in patients with CSME.

TREATABLE LESIONS

1. Focal leaks situated more than 500 microns away from the centre of macula causing hard exudates or retinal thickening.
2. Focal leaks situated within 300- 500 microns from centre of macula causing hard exudates or retinal thickening.
3. Areas having diffuse leakage from capillaries and microanuerysms.

4. Capillary avascular areas other than foveal avascular zone not treated previously.

Modified ETDRS Focal/Grid laser photocoagulation of CSME.

1. Do not treat lesions situated closer than 500 microns from the fovea
2. Avoid intense and excessively dense laser burns
3. Do not treat intra or pre retinal hemorrhages.
4. Large microanuerysms that appear the main cause of leakage must be treated focally to the ETDRS end point of colour change(either whitening or darkening).

TECHNIQUE OF FOCAL LASER

All the leaking microanuerysms are treated directly using a spot size of 50-100microns for duration of 0.1 sec.

TECHNIQUE OF GRID LASER

Areas of diffuse leakage without any identifiable focal areas of leakage are treated . Spot size used is 50-100 microns and a grid pattern of light intensity equally spaced burns is produced. 2 burns are placed at a distance of one burn width.

LASER TYPES USED

Most commonly used wavelength is 514 nm and 810 nm infrared diode laser.

MEDICAL MANAGEMENT OF CSME

a. Intravitreal Steroids

Steroids are beneficial in treatment due to their anti-inflammatory properties**.** Intravitreal steroids have been used in patients who had refractory CSME**.** Intravitreal triamcinolone 4mg/0.1ml alone or combination with laser has been studied in various therapeutic investigations. Side effects include cataract, iop raise, endophthalmitis and retinal detachment[33].

b. Intravitreal Anti Vascular Endothelial Growth Factors (VEGF)

VEGF[34] has inflammatory properties and is found to play a role in pathogenesis of DME by increasing capillary permeability. Anti VEGF agents help in restoring the normal permeability of blood retinal barrier. Bevacizumab , recombinant, humanized , monoclonal antibody against VEGF has been used in diffuse type of macular edema where other treatment have failed.

Dosage used is 1.25mg/0.05ml. However it has transient effect and has to be repeated at interval of 4-6 weeks.

Pegatinib sodium (Macugen) 1.3mg/0.05ml 3 injections are given at an interval of 6 weeks and followed for 36 weeks. Its specifically neutralises VEGF165.

Ranibizumab is humanized, recombinant monoclonal antibody fragment. Injected intravitreally it inhibits all forms of VEGF.

OTHER PHARMACOLOGICAL AGENTS UNDER STUDY

1. Aldose reductase inhibitors- Sorbinil, Ponalrestat,Tolrestat act by inhibiting aldose reductase enzyme responsible for conversion of glucose to Sorbitol. These agents help in slowing development of DR.
2. Protein kinase inhibitors – Ruboxistaurin acts by inhibiting protein kinase c beta which plays a role in pathogenesis of CSME.
3. Advanced glycation end products inhibitors and antioxidants

SURGICAL MANAGEMENT OF CSME

CSME with evidence of taut posterior hyaloid or posterior hyaloidal traction are benefited by performing parsplana vitrectomy and detachment of posterior hyaloid. CSME not responding to laser may be benefited by performing vitrectomy with or without membrane peeling[35].

AIM OF THE STUDY

PRIMARY OBJECTIVE

To analyze the patterns of structural changes in clinically significant diabetic macular edema in patients with diabetic retinopathy by optical coherence tomography.

SECONDARY OBJECTIVE

1. To quantitatively asses the central foveal retinal thickness by optical coherence tomography in patients with clinically significant diabetic macular edema.
2. To study the profile of diabetic patients with clinically significant macular edema

MATERIALS AND METHODS

METHODOLOGY

1. Diabetic patients with recently detected clinically significant macular edema by fundoscopic examination are included in the study
2. These patients are subjected to optical coherence tomography
3. Patterns of macular edema and retinal thickness is studied

INCLUSION CRITERIA

All the patients with clinically significant macular edema which was defined if one or more of the following criteria were met (ETDRS criteria)

1. Retinal thickening within 500 microns of centre of macula
2. Exudates within 500 microns of centre of the macula if associated with retinal thickening
3. Retinal thickening of one disc diameter any part of which is within one disc diameter of centre of the macula

EXCLUSION CRITERIA

1. Patients with macular edema due to any other cause
2. Patients with diabetic retinopathy who had undergone any form of treatment – Grid /PRP
3. Patients with diabetic nephropathy

4. Patients with associated hypertension
5. Patients with media opacities

EXAMINATION

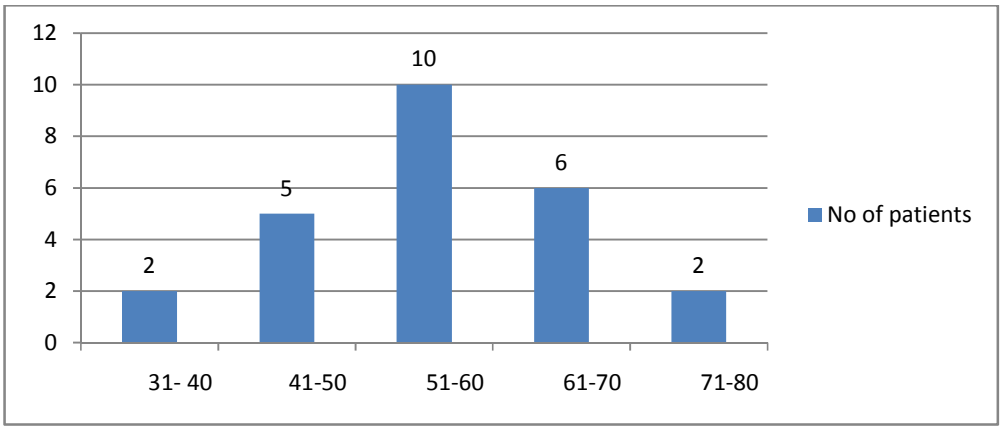
A brief history about the type, duration of diabetes, associated hypertension, renal problems, past history of any treatment was taken. IOP was measured using applanation tonometry, RBS, Urine albumin and sugar were estimated, Visual acuity was assessed using the Snellen's chart. Anterior segment examination was done with slit lamp biomicroscopy. Posterior segment evaluation was done with 90D/78 D lens with slit lamp bio microscopy and binocular indirect ophthalmoscope. Fundus fluorescein angiography and optical coherence tomography was done for all patients.

OBSERVATION AND ANALYSIS

1. AGE DISTRIBUTION

Table 1

Age group (years)	No of patients	Percentage
31- 40	2	8%
41-50	5	20%
51-60	10	50%
61-70	6	24%
71-80	2	8%

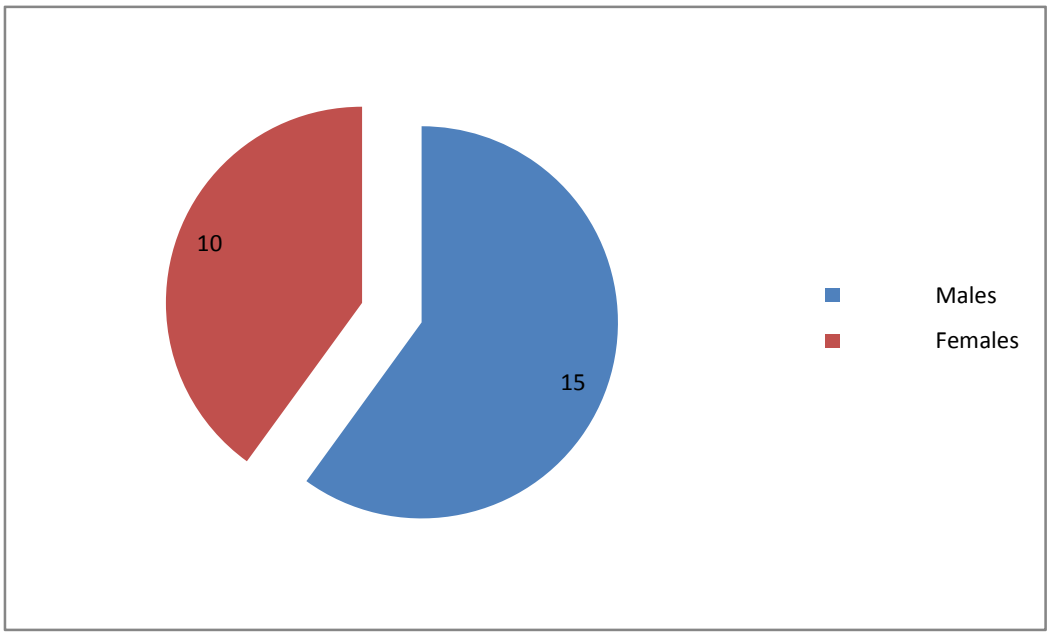


As seen above in our study 20% of the patients were in 41-50 years age group, 40% in 51-60 years age group, and 24% in 61-70 years age group. Middle aged population i.e between 41- 60 years had highest prevalence of the DR which correlates with the WESDR.

2. SEX DISTRIBUTION

Table 2

Sex	No of patients	Percentage
Males	15	60%
Females	10	40%

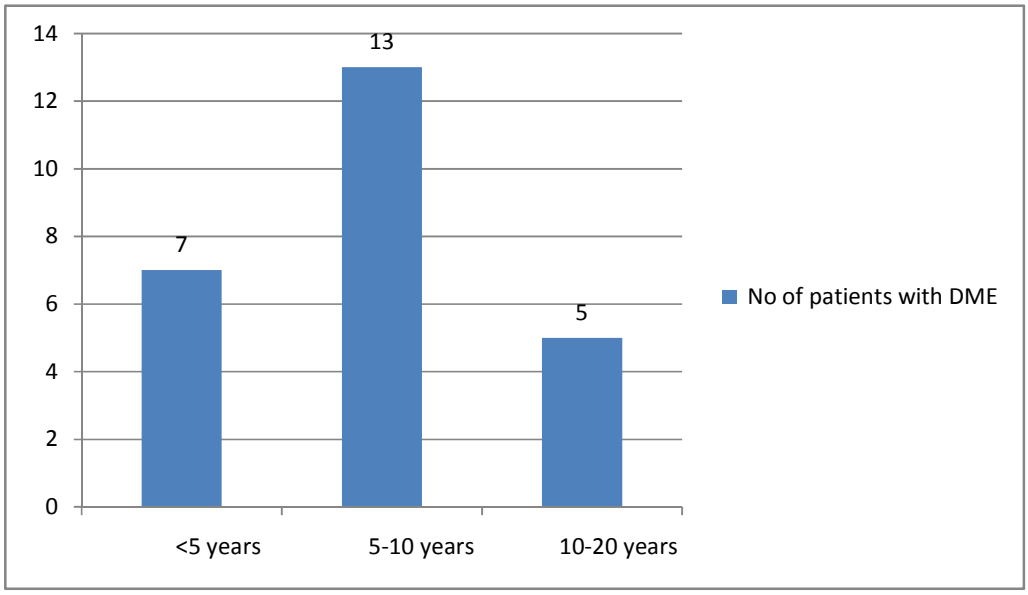


Males were the predominant sex affected in our study i.e 60 %. This observation correlates with that of Wisconsin Epidemiological study of diabetic retinopathy which showed a male to female ratio of 1.5:1

3. DURATION OF DIABETES

Table 3

Duration	No of patients with DME	Percentage
<5 years	7	28%
5-10 years	13	52%
10-20 years	5	20%



1. In our study the incidence Of DME with duration of <5 years was 28%

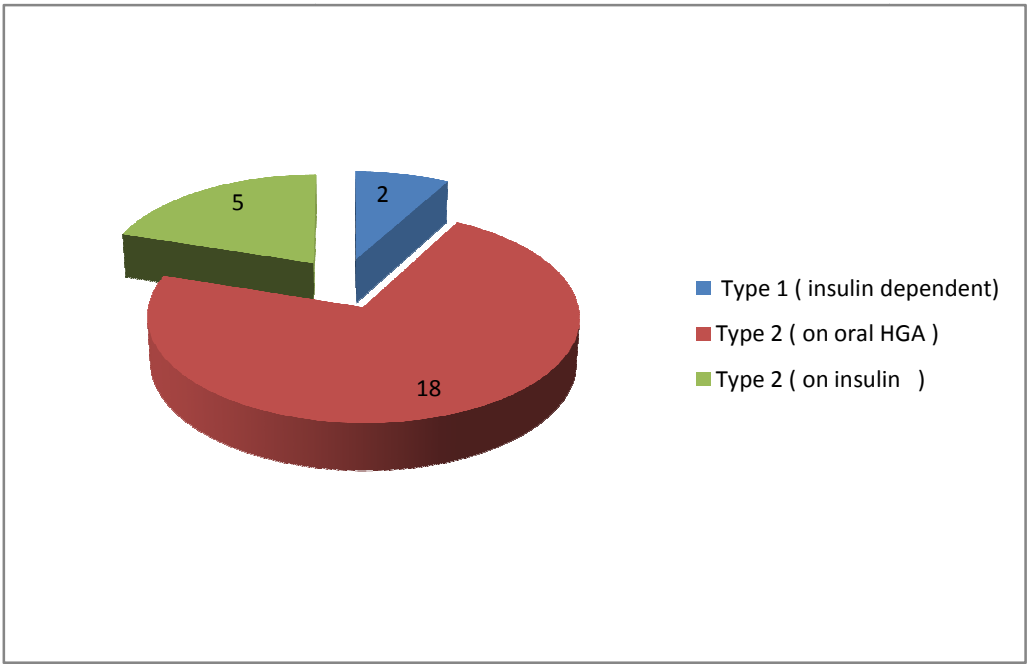
2. Incidence of DME in patients with duration of 5 – 10 years was 52%

3. Incidence of DME in patients with duration of10 – 20 years was 20%

4. TYPE OF DIABETES

Table 4

Type	No of patients	Percentage
Type 1 (insulin dependent)	2	8%
Type 2 (on oral HGA)	18	72%
Type 2 (on insulin)	5	20%

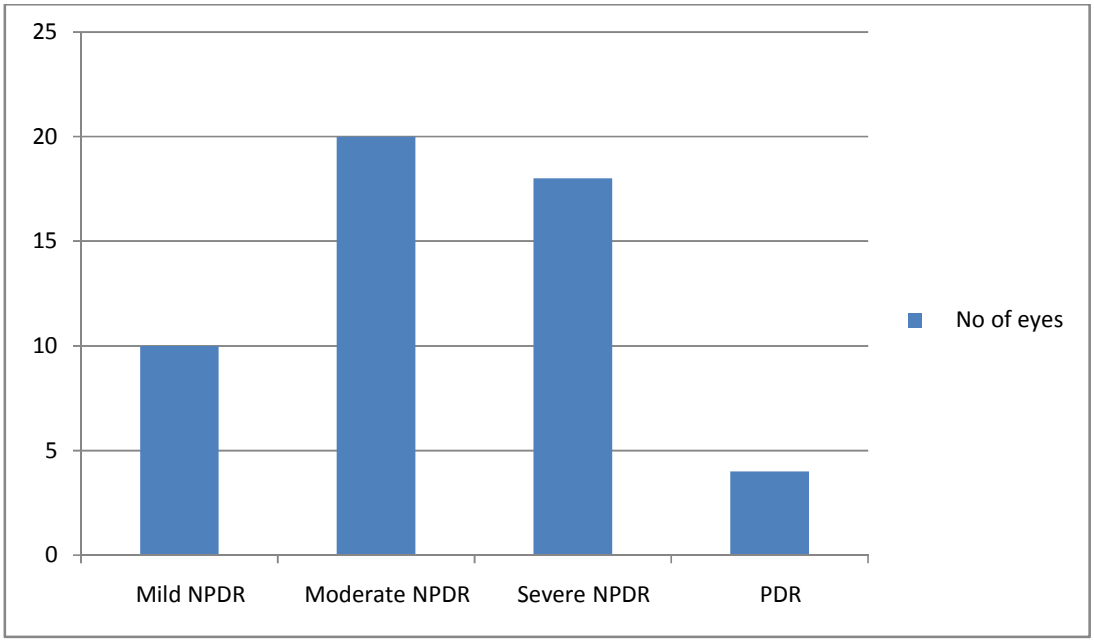


In our study 8% of patients were type 1 diabetics, 72% of patients were type 2 diabetics who were on oral hypoglycaemic agents and 20 % were type 2 diabetics on insulin therapy.

5. TYPE OF DIABETIC RETINOPATHY

Table 5

Type of DR with CSME	No of eyes	Percentage
Mild NPDR	10	20%
Moderate NPDR	20	40%
Severe NPDR	18	36%
PDR	4	8%

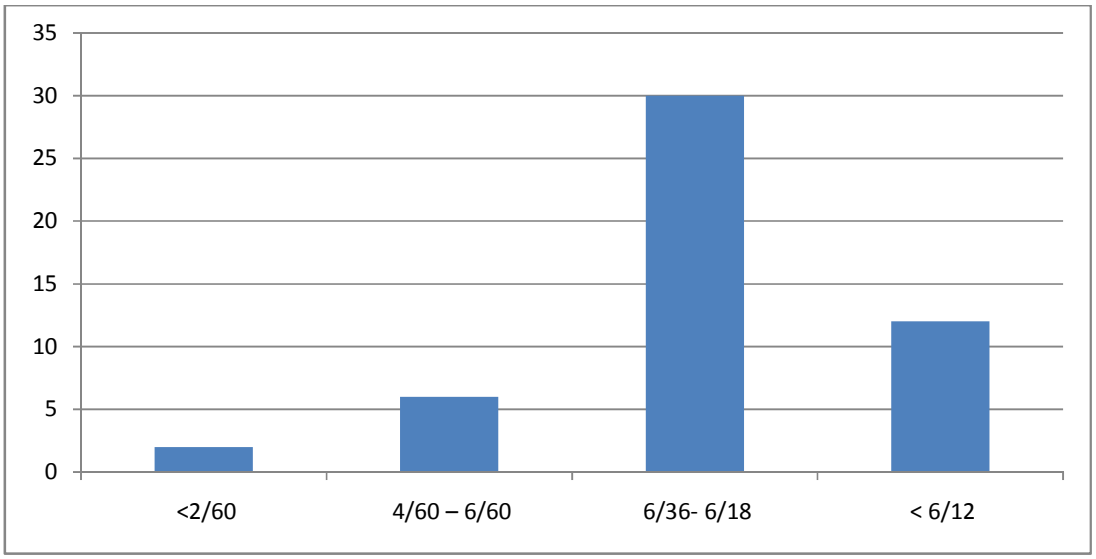


In our study 20% of the eyes had mild NPDR, 40% moderate NPDR, 36% had severe NPDR and 8% had PDR

6. VISUAL ACUITY

Table 6

Visual acuity	No of eyes
<2/60	2
4/60 – 6/60	6
6/36- 6/18	30
< 6/12	12

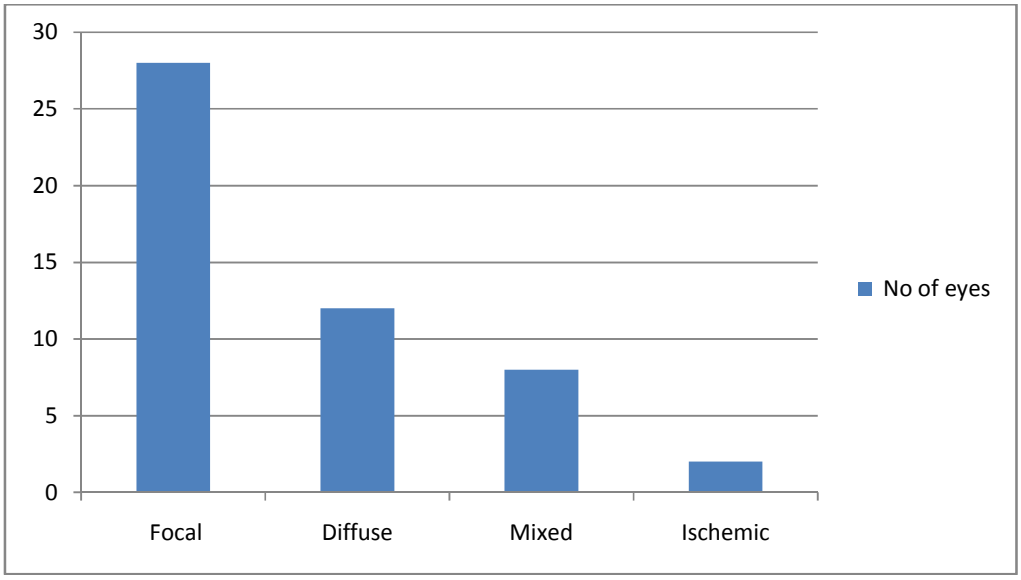


30 eyes in our study had a visual acuity ranging from 6/36-6/18 and 12 eyes had VA of < 6/12. 12 eyes had visual acuity of < 2/60

7. FFA PATTERNS

Table 7

Type	No of eyes
Focal	28
Diffuse	12
Mixed	8
Ischemic	2

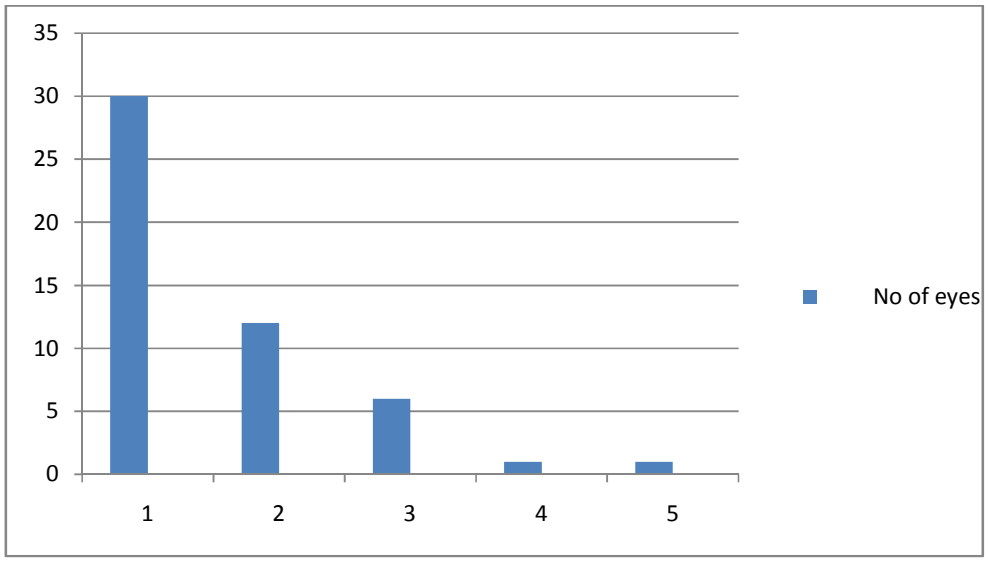


In our study 28 eyes had focal pattern of leakage in FFA, 12 had diffuse pattern, 8 had mixed pattern and 2 eyes had ischemic type of maculopathy.

8. OCT TYPES

Table 8

Type	No of eyes
Spongy	30
CME	12
CME with serous detachment	6
Vitreomacular traction (VMT)	1
Taut posterior hyaloid (TPH)	1

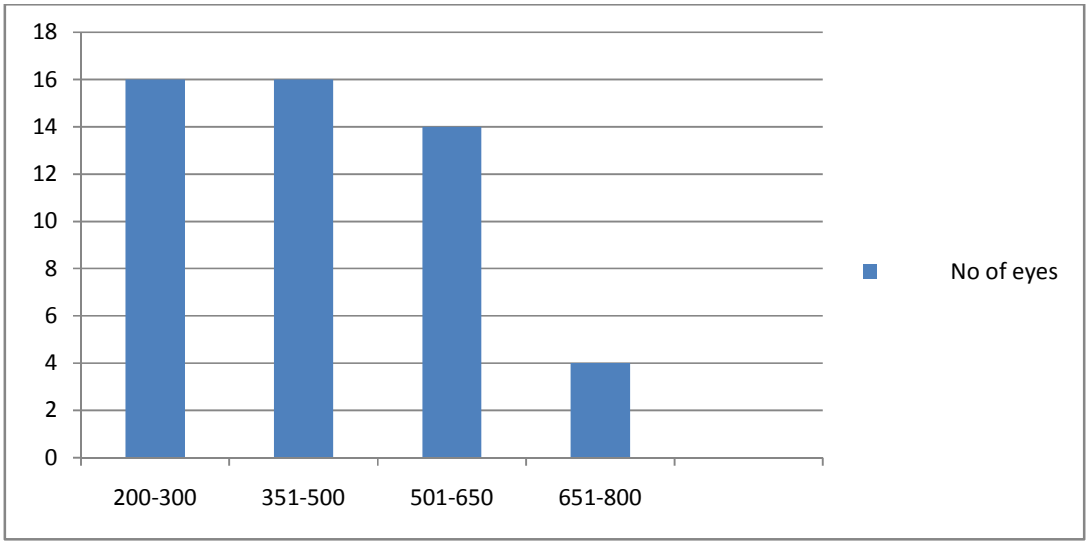


In our study 30 eyes had a spongy pattern in OCT, 12 had CME, 6 had CME with serous detachment, VMT and TPH was present in one eye each.

9. RETINAL CENTRAL FOVEAL THICKNESS BY OCT

Table 9

Thickness in microns	No of eyes
200 - 350	16
351- 500	16
501-650	14
651-800	4

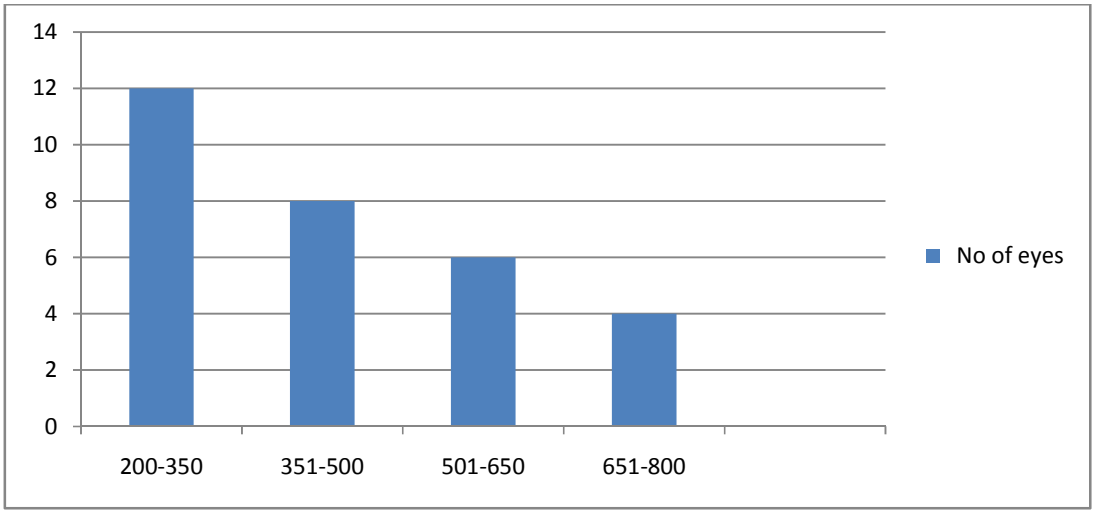


18 eyes in our study were found to have a thickness between 200 and 350, 14 had a thickness between 351 – 500 and 14 had a thickness within the range of 501-650, 4 eyes had thickness between 651 and 800.

10. RETINAL CENTRAL FOVEAL THICKNESS IN SPONGY TYPE OF CSME

Table 10

Thickness in microns	No of eyes
200 - 350	12
351- 500	8
501-650	6
651-800	4

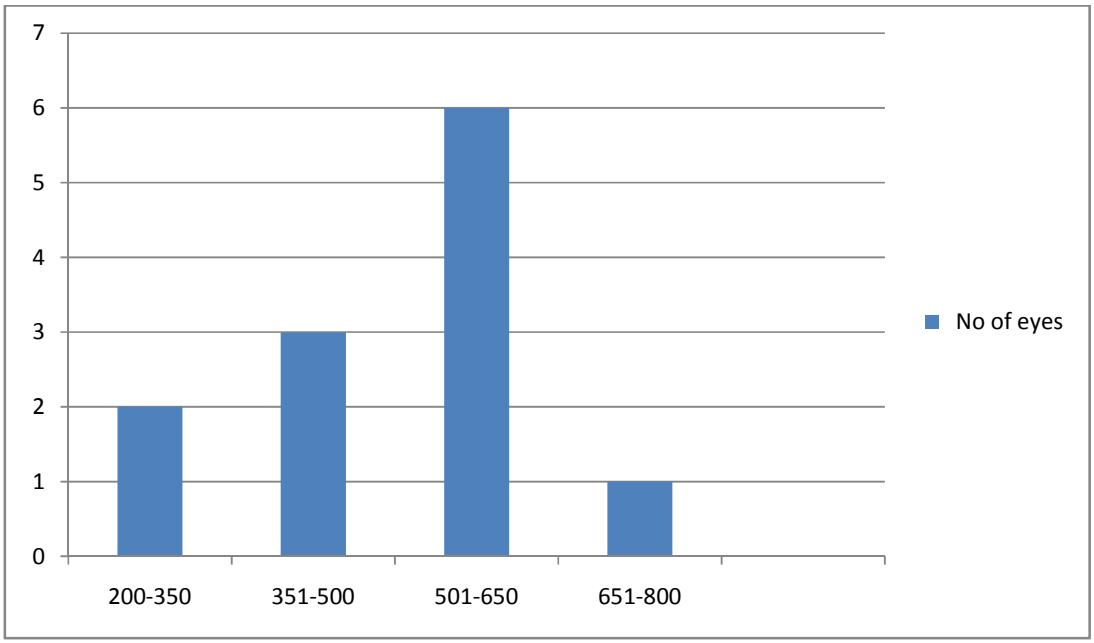


In spongy pattern of CSME 12 eyes had thickness in range of 200 – 350 ,8 had thickness in range of 351 – 500 , 6 eyes had in range of 500-650 , 4 in range of 651- 800 .

11. RETINAL CENTRAL FOVEAL THICKNESS IN CME

Table 11

Thickness in microns	No of eyes
200 - 350	2
351- 500	3
501-650	6
651-800	1
801-950	0

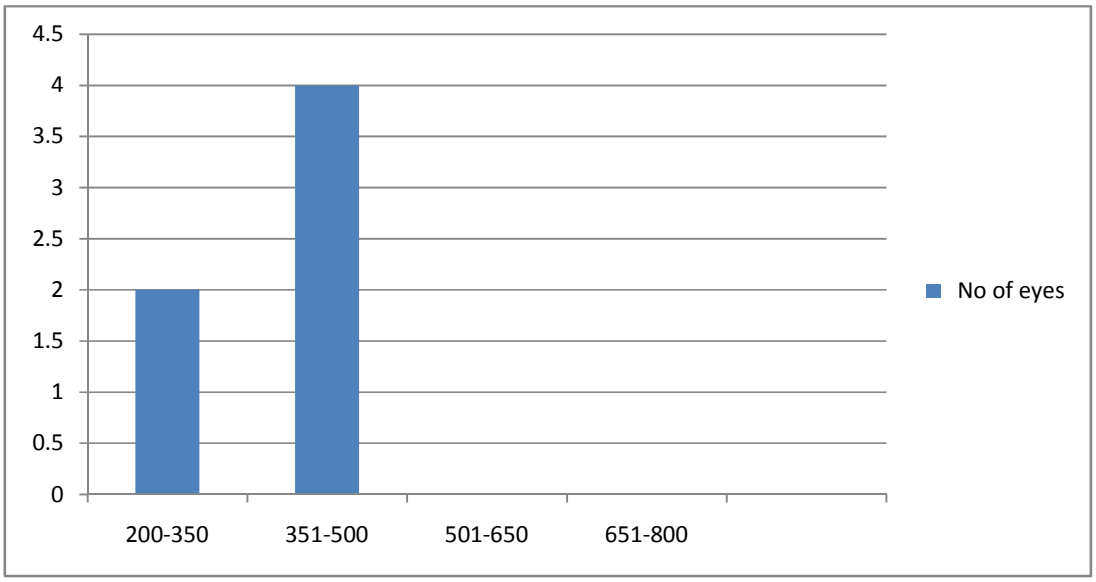


In cystoid pattern of CSME 2 eyes had thickness in range of 200 – 350 ,3 had thickness in range of 351 – 500 , 6 eyes had in range of 500-650 , 1 in range of 651- 800 .

12. RETINAL CENTRAL FOVEAL THICKNESS IN CME WITH SEROUS DETACHMENT

Table 12

Thickness in microns	No of eyes
200 - 350	2
351- 500	4
501-650	0
651-800	0
801-950	0

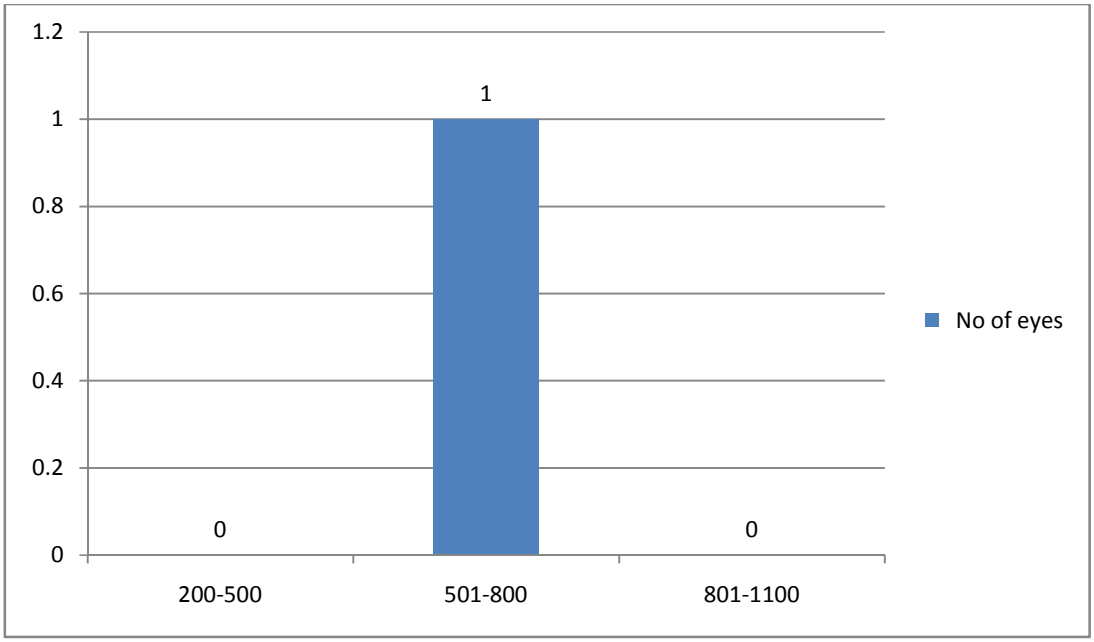


In 6 eyes of CME with SRD pattern of CSME 4 eyes had retinal thickness in range of 200 – 350 and 2 had thickness in range of 351 – 500.

13. RETINAL CENTRAL FOVEAL THICKNESS IN VMT PATTERN OF CSME

Table 11

Thickness in microns	No of eyes
200 - 500	0
501-800	1
801-1100	0

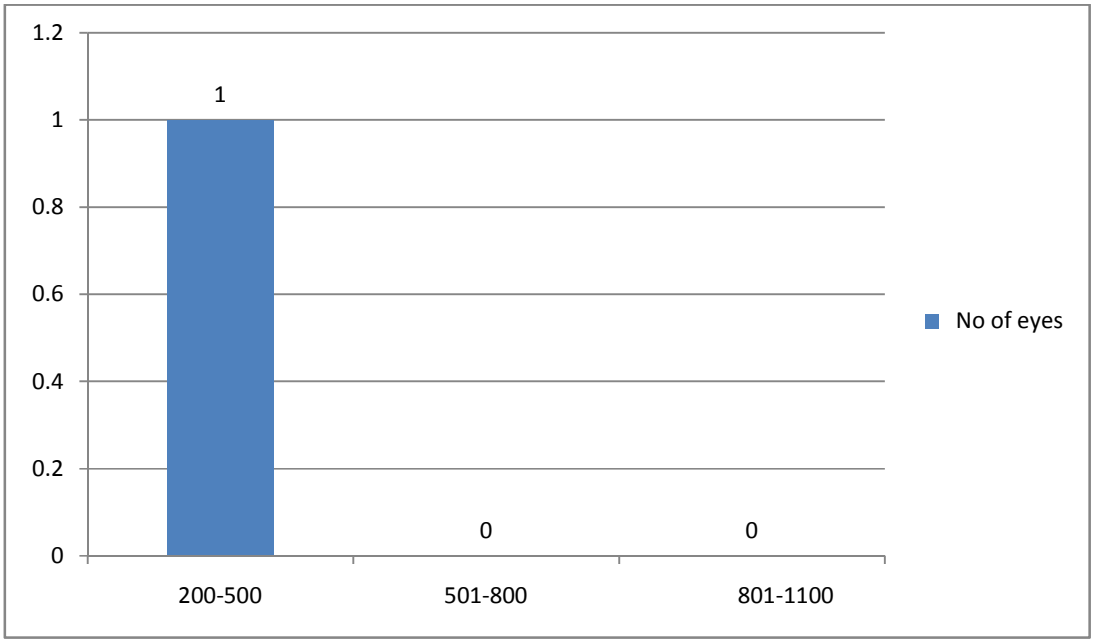


In our study the vitreomacular traction pattern of CSME had a thickness of 554 microns

14. RETINAL CENTRALFOVEAL THICKNESS IN TPH PATTERN OF CSME

Table 14

Thickness in microns	No of eyes
200 - 500	1
501-800	0
801-1100	0

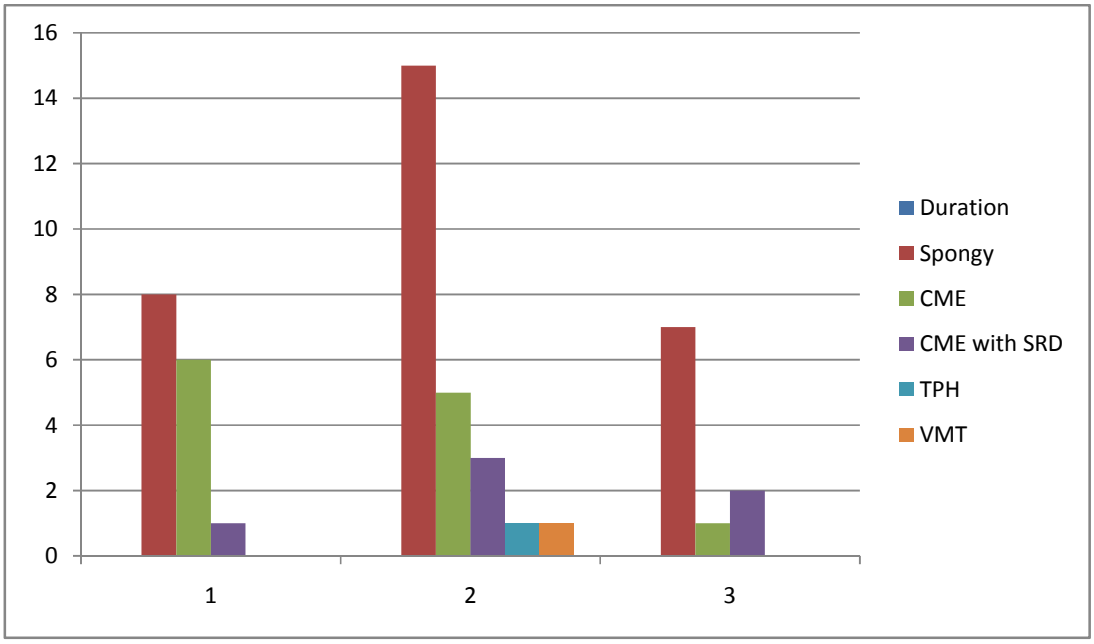


In our study the taut posterior hyaloids pattern of CSME had a thickness of 496 microns

15. CORRELATION BETWEEN DURATION OF DM AND OCT PATTERNS

Table15.

Duration	Spongy	CME	CME with SRD	VMT	TPH
<5 years	8	6	1	0	0
5-10 years	15	5	3	1	1
11-20 years	7	1	2	0	0

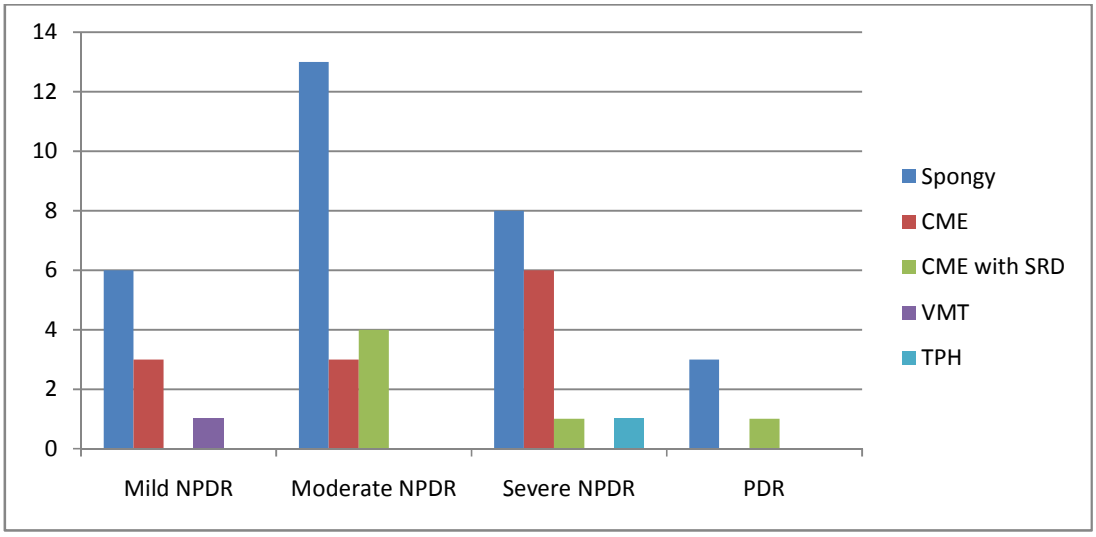


In our study the spongy pattern of CSME was most common across the 3 groups followed by the CME and CME with serous detachment.

16. CORRELATION BETWEEN SEVERITY OF DR WITH OCT PATTERNS

Table 16

Severity	Spongy	CME	CME with SRD	VMT	TPH
Mild NPDR	6	3	0	1	0
Moderate NPDR	13	3	4	0	0
Severe NPDR	8	6	1	0	1
PDR	3	0	1	0	0

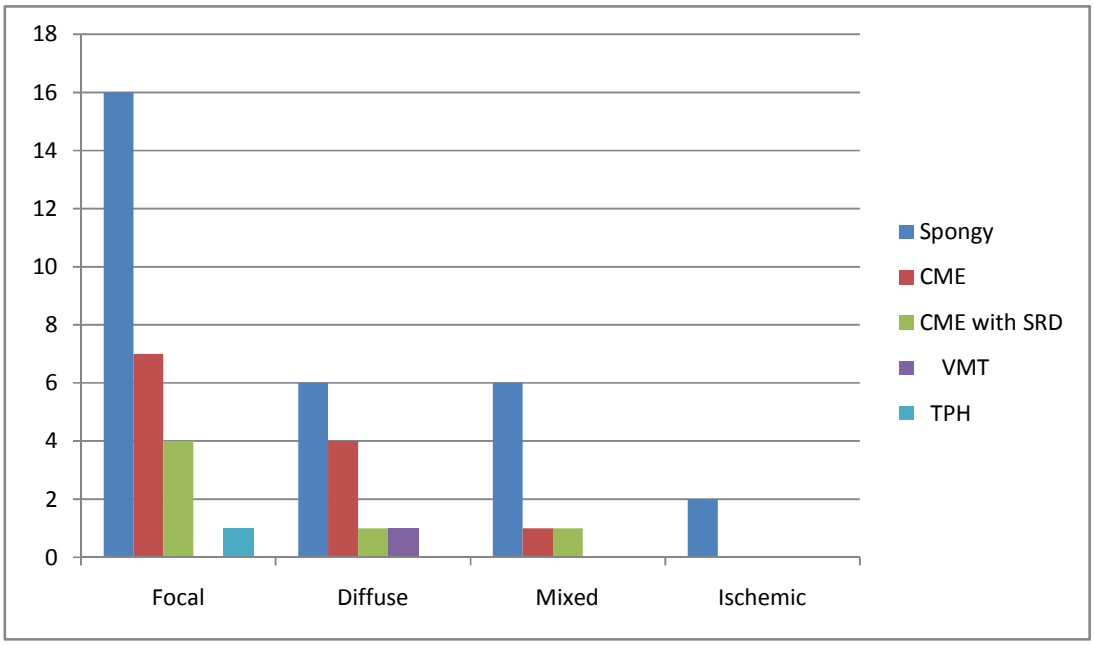


In our study spongy pattern of CSME was found to be commonest in all types of DR. CME more common in severe NPDR patients in our group and CME wit SRD was commoner in moderate NPDR

17. CORRELATION BETWEEN FFA PATTERN AND OCT PATTERN OF CSME

Table 17

FFA pattern	Spongy	CME	CME with SRD	VMT	TPH
Focal	16	7	4	0	1
Diffuse	6	4	1	1	0
Mixed	6	1	1	0	0
Ischemic	2	0	0	0	0

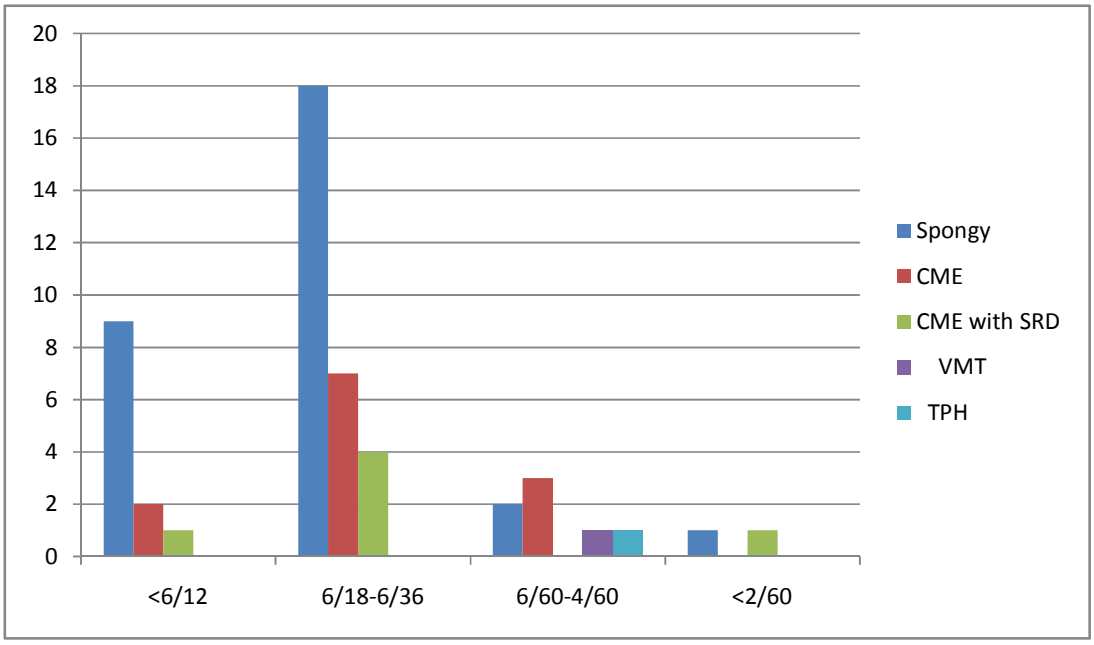


In our study spongy, CME and CME with SRD pattern of CSME were more commonly associated with focal leaks on FFA.

18. VISUAL ACUITY AND OCT PATTERN

TABLE 18

Visual acuity	Spongy	CME	CME with SRD	VMT	TPH
<6/12	9	2	1	0	0
6/18-6/36	18	7	4	0	0
6/60-4/60	2	3	0	1	1
<2/60	1	0	1	0	0



60% of the patients with spongy pattern and CME pattern of CSME had visual in the range of 6/18-6/36. Visual acuity of less than 2/60 was observed in 2 eyes.

DISCUSSION

our study included 50 eyes of 25 diabetic patients with CSME and varying degrees of severity of diabetic retinopathy.

a. In our study majority of the patient's i.e 15 patients were in the age group of 41 – 50 years of age. The Wisconsin Epidemiological study[25] of Diabetic retinopathy revealed that middle aged population are more affected by DR and have a higher prevalence of DR. Our findings correlate with the study findings.
b. Males were the predominant sex to be affected in our study (60 %) which correlates with the findings of the Wisconsin Epidemiological study of Diabetic retinopathy[25] which suggested a male to female ratio of 1.5:1
c. 28 % of the patients in our study had duration of diabetes of less than 5 years, 52% had duration of 5 – 10 years and 20 % had a duration of 10 -20 years.
d. In our study 2 patients (8%) had type 1 diabetes mellitus who were on insulin, 18(72%) patients had type 2 DM on OHA and 5(20%) patients were type 2 DM patients on insulin.

e. CSME was associated with mild NPDR in 10 eyes (20%), moderate NPDR in 20 eyes (40%), and severe NPDR in 16 eyes (32%). PDR was seen in only 4 eyes (8%) in our study.

f. Visual acuity of < 6/12 was seen in 12 eyes (24%), Visual acuity between 6/18 -6/36 in 29 eyes (58%), 7 eyes (14%) had VA between 6/60 -4/60, 2 eyes (4%) had VA of less than 2/60.

g. On fundus fluorescein angiography focal pattern of diabetic maculopathy was noted in 28 eyes(56%), diffuse pattern of diabetic maculopathy in 12 eyes(24%) ,mixed pattern of diabetic maculopathy in 8eyes(16%) and 2 eyes(4%) had ischemic type.

h. On performing OCT spongy pattern of CSME was noted in 30 eyes (60%), cystoid pattern in 12 eyes (24%), cystoid pattern with serous retinal detachment was noted in 6 eyes (12%), Vitreomacular traction and taut posterior hyaloids was identified in one eye each. The spongy pattern of diabetic macular edema was found to be the predominant form[36] of structural type of DME in patients of our study group. This correlates with the study conducted and presented in AIOS by Anush goyal[37] et al.

i. In our study 16 eyes (32%) had central foveal thickness in the range of 200-350, 16 eyes (32%) had thickness in the range of 351-500, 14 eyes (28%) had central foveal thickness in the range of 501-650,

and 4 eyes (8%) had central foveal thickness in range of 651-800 microns.

j. In the group with spongy pattern of CSME 12 eyes (40%) had a central foveal thickness in range of 200 -350, 8 eyes (27%) in range of 351-500, 6eyes (20%) in the range of 501 – 650, 4 eyes (13%) in 651-800 micron range.

k. In the group with cystoid pattern of CSME, 2 eyes(17%) had a central foveal thickness in range of 200- 350 microns, 3 eyes(25%) in 351-500 range, 6eyes(50%) in 501-650 range and 1(8%) in 651-800 micron thickness range.

l. 2 eyes (34%) in group of cystoid with serous detachment pattern had central foveal thickness in range of 200 -350 microns and 4 eyes (66%) in range of 351-500 microns.

m. One eye with VMT pattern had a central foveal thickness of 554 microns and one eye with taut posterior hyaloids had foveal thickness of 496 microns.

n. Mean central foveal thickness in normal individual is 182 +/- 23 microns[24,1]. In our study group the mean central foveal thickness was 454 +/- 138 microns. This difference in retinal thickness between normal individual and patient with clinically significant DME was found to be highly significant ($p<0.002$).

o. Spongy pattern of CSME was found to be the commonest pattern in all groups of patients who were classified depending on duration of DM.

   Eyes with DM of <5 years had spongy pattern in 8eyes (54%). CME in 6 eyes (40%) and 1 eye (6%) had CME with SRD.

   Eyes with DM of 5 – 10 year duration had spongy type in 15 eyes (60%), CME in 5eyes (20%), CME with SRD in 3 eyes (12%) and VMT and TPH in one eye each. In eyes with DM of >10 years spongy type was seen in 7 eyes (70%), CME in 2 eyes (20%), and one eye (10%) had CME with SRD.

p. Mild NPDR was seen in 10 eyes, 6 eyes (60%) were of spongy pattern and3 eyes (30%) of CME pattern. Moderate NPDR was seen in 20 eyes, 13 eyes (65%) of spongy pattern, 3 eyes (15%) and 4 eyes (20%) of CME with SRD. Severe NPDR was present in 16 eyes, 8 eyes (50%) were of spongy pattern, 6 eyes (38%) of CME pattern and 1 eye (6%) each of CME with SRD and TPH. PDR was seen in 4 eyes, 3 were of spongy pattern (75%) and one eye was of CME with SRD.

q. Focal pattern of leakage on FFA was predominantly associated with spongy type of CSME pattern (54%). 28 eyes had focal leakage out

of which 16 (58%) were spongy, 7(25%) were CME,4 (14%) were CME with SRD and one eye had TPH.12eyes had diffuse pattern out of which 6 (50%) were spongy pattern , 4 (34%) were CME pattern , one eye(8%) each were of CME with SRD and VMT. Mixed leakage was seen in 8 eyes, 6 (76%) was of spongy pattern and one each of CME and CME with SRD.

Two eyes had ischemic pattern both of which had spongy pattern in OCT.

r. 11 eyes had visual acuity of <6/12, 9 were associated with spongy, 2 with CME and 1 eye had CME with SRD. 29 eyes had visual acuity between 6/18-6/36, 18 had spongy pattern (62%), 7 had CME (24%), 4 had CME with SRD (14%).7 eyes had visual acuity between 6/60-4/60, 2 had spongy pattern (28%), 3 had CME (42%) and one each had VMT and TPH. Visual acuity of less than 2/60 was seen in 2 eyes, one had spongy pattern and other had CME with SRD.

CONCLUSION

In our study 50 eyes of 25 patients was studied.

On OCT spongy pattern of CSME was found to be the commonest pattern (60%) followed by CME (24%), CME with SRD (12%). VMT and TPH was least common pattern (2%).

Spongy pattern had an average central foveal thickness of 412 microns, CME pattern had average central foveal thickness of 504 microns and CME with SRD had average central foveal thickness of 409 microns. Average central foveal thickness in all the eyes of CSME was 454+/-136 microns which was statistically significant when compare to central foveal thickness of normal individuals.

Moderate NPDR was commonest type of DR in eyes with spongy (41%) and CME with SRD pattern of CSME (66%). Severe NPDR was the commonest type of DR in cystoid pattern (50%) in our study group.

Focal maculopathy was the commonest FFA pattern associated with spongy (54%), CME (59%) and CME with SRD (66%). Majority of eyes with spongy (60%), CME (58%) and CME with SRD (66%) had visual acuity between 6/18-6/36. Two eyes had visual acuity less than 2/60.

Middle aged group i.e between 41- 60 years is found to be having the greatest incidence of diabetic maculopathy. Males were found to be affected predominantly. Incidence of diabetic retinopathy was found be higher in patients who had diabetes for a longer duration. Majority of the patients in our study group were type 1 diabetics on OHA.

OCT greatly facilitates the study of retinal foveal anatomy and thickness by providing a high resolution cross sectional images of the retina. Also subtle macular edema that may be difficult to detect on slit lamp examination can be easily detected by OCT. FFA helped to determine the specific pattern of leakage which helps in determining the type of laser treatment.

Determining the type of CSME and retinal thickness by OCT helps in determining the mode of treatment and treatment response in these patients.

BIBILOGRAPHY

1. Retinal diseases and OCT – Travis A Meredith , sandeep saxena.
2. ME Breezinski, B Boumaet al. Optical biopsy and OCT. Ann N Y Acad SCI 1998; 9:838:68-74
3. AF Fercher.Optical coherence tomography. J Biomed Opt. 1996:1:157-173
4. Davis den, Carr s. Optical coherence domain reflectometry. Opt LETT 1987;12;158-160,
5. Hee ,Huang d, Swanson EA et al. High speed optical coherence domain reflectometry. Opt Lett 1992;16:151-153.
6. I muller, (ED): Optical instruments for biomedical laser applications. Vol 658.SPIE;1986:48-51.
7. Hiram G.; Costa, Marco A.; Guagliumi, Giulio;, Andrew M.; Simon, Daniel I. (November 2009). "Optical coherence tomography and intracoronary care JACC": Cardiovascular Interventions **2** (11): 1035–1046
8. W wwalecki, P Wei, W Van, K Lai, A Lee, Interferometric Metrology for Thin and Ultra-Thin Compound Semiconductor Structures . , CS Mantech Conference, 2004
9. Swansen A, Hee Mr et al.Science of opticl coherence tomography.119;255:1176-1180

10. Atlas of Optical coherence tomography –Gupta Amod, Dogra MR, Gupta Vaishali.
11. CR Youngquist , S carr. A new optical evaluation technique – optical coherence tomography. Optt Lett 1995;113;325-332
12. Jafe Gj , Capolli j. Detection and management of retinal diseases by OCT Am j OPH 2003 ;137; 156-159
13. Spectoral domain OCT – Dacosta Shaun, Rajendran Babu, Janakiraman .
14. AC toth, Narayan DG et al. Human retinal imaging by OCT. Arch Ophthal 1995;113;325-332
15. New investigations in ophthalmology – Taneja Dada, Subarta Mandal.
16. MR Hee, CA Puliafito. Optical imagining of ocular diseases.
17. W Drexler, Morgner U et al .In vivo ultrahigh resolution OCT of retina.Opt Lett 1999;24;1221-1223.
18. W Drexler,Herman B et al. Enhanced visualisation of macular pathology using ultrahigh resolution optical coherence tomography Arch Ophthalmol 2003;121:695-706
19. B cense, NA Nasiff et al.Ultrahigh resolution optical coherence tomography using spectoral domain technology. Optics Expr 2004;12:2112-2119.

20. Caproli J, jaffe GJ.Detection and management of retinal disease and glaucoma by optical coherence tomography.
21. Aiello LP, Gardner TW, King GL, , Ferris FL 3rd, et al. Diabetic retinopathy. Care of diabetes1998; 21 : 143-56.
22. Klein R, Klein BE, Moss SE. Visual impairment in diabetes, Ophthalmology 1986; 91 : 1-9.
23. Reema M, Prem kumar S, Anitha B, Prevalence of diabetic retinopathy in urban India;Chennai Urban Rural Epidemiology Study (CURES) Eye Study, Invest Ophthalmol Vis Sci 2005; *46* : 2328-33.
24. Jack J Kanski . Clinical and systematic approach edition 6 573-576.
25. Wisconsin epidemiological study of diabetics retinopathy Arch Ophtamol 1984;102;520-526
26. Early Treatment Diabetic Retinopathy Study Research group. Grading diabetic retinopathy severity from stereoscopic colour fundus photograph.Ophthalmology 1991;95:786-806.
27. Effect of pregnancy on microvascular complications in diabetes control and complication trial.The diabetes control and complication Trial Research Group. Diabetes care 2000;23:1084-91.
28. UK Prospective Diabetes Study group. Effect of intensive control of blood pressure on diabetic retinopathy.Lancet;1996:352:854-856.
29. Natham DM,Glynn RJ. Correlation between serum lipid level and risk od diabetic macular edema. Diabetes 2004 53;2863:2892.

30. Krepler, Bowski et al. Catract surgery in patients with diabetic retinopathy. Incidence , progression and visual outcome in diabetic macular edema.Clin Exp Ophthamol 2002;240:735-738.
31. Early Treatment Of Diabetic Retinopathy study Research group.Diabetic macular edema and photocoagulation. Study report no 1 Arch Ophthal 1985; 103;1796-1806.
32. UK prospective Diabetes Study (UKPDS). Progress and performance . Diabetologia. 1991; 98; 823-833.
33. Wilon ca, yando n, handa jt . Treatment with intravitreal steroids reduces breakdown of blood retinal barrier due to laser photocoagulation. Arch Ophthamol 1992;110:1115-9.
34. Shah SM,Tatlipar S et al . Role of vascular endothelial growth factor in diabetic macular edema.Am J Ophthamol 2006;142:961-9.
35. Medrith TA; The diabetic retinopathy vitrectomy study. In Ryan SJ, ed Retina volume 2 1998 ; 37-48.
36. Otani T, Kishi S, Maruyama Y. Diabetic macular edema and optical coherence tomography patterns Am J Ophthalmol. 1999Jun; 127(6):688-93.
37. Anush Goyal et al AIOC 2010.

PROFORMA

Serial no

Name

Age

Sex

OP No

Occupation

History

Complaints

1. Defective vision
2. Pain in the eye
3. Field defects

Past history

1. Diabetes - Type, duration, on OHA/inj insulin
2. Hypertension – Duration, medication

Family history

Systemic examination

Pulse rate

Blood pressure

RBS

Urine alb and sugar

Ocular examination

		RE	LE
Visual acuity	-		
Conjunctiva	-		
Cornea	-		
Anterior chamber	-		
Iris	-		
Pupils	-		
Lens	-		
Tension (applanation tonometry)	-		
Fields by tangent screen	-		
Colour vision (Ishihara chart)	-		
Fundus examination			
By direct ophthalmoscopy	-		
By indirect ophthalmoscopy	-		
Fundus fluorescein angiography	:	Type of leak	
Optical coherence tomography	:	Type of CSME	
		Macular thickness	

KEY TO MASTER CHART

VA	-	Visual acuity
NPDR	-	Non proliferative diabetic retinopathy
PDR	-	Proliferative diabetic retinopathy
CSME	-	Clinically significant macular edema
FFA	-	Fundus fluorescein angiography
OCT	-	Optical coherence tomography
RE	-	Right eye
LE	-	Left eye
VMT	-	Vitreomacular traction
TPH	-	Taut posterior hyaloids
CME	-	Cystoid macular edema

MASTER CHART

Name	Age	Sex	Duration of DM in years	Type of DM	Diagnosis		visual acuity		FFA pattern		Oct pattren		Central foveal thickness in microns	
					RE	LE	RE	LE	RE	LE	RE	LE	RE	LE
Vargees	43	F	2	Type 2 OHA	Moderate NPDR/CSME	Mild NPDR/CSME	6/36 PH 6/24	6/36 PH6/12	Mixed	Focal	Spongy	Spongy	480	456
Ramaswamy	56	M	7	Type 2 OHA	PDR/CSME	Moderate NPDR/CSME	6/12 PH 6/9	2/60 NIP	Focal	Focal	Spongy	Cysoid with SRD	226	464
Gopi	45	M	3	Type 2 OHA	Mild NPDR/CSME	Moderate NPDR/CSME	6/24 PH 6/18	4/60 PH 6/60	Diffuse	Ischemic	Spongy	Spongy	512	210
Parvathi	54	F	4	Type 2 OHA	Moderate NPDR/CSME	Severe NPDR/CSME	6/9 PH 6/6	6/36 PH 6/24	Focal	Focal	Spongy	Cysoid with SRD	254	357
Prabhakar	41	M	1	Type 2 OHA	Severe NPDR/CSME	Mild NPDR/CSME	6/24 NIP	6/18 NIP	Diffuse	Diffuse	Cystoid	Cystoid	541	287
Raja	60	M	9	Type2 insulin	Severe NPDR/CSME	PDR/CSME	6/9 NIP	6/24 NIP	Focal	Focal	Cystoid	Spongy	265	411
Antonioammal	51	F	3	Type 2 OHA	Severe NPDR/CSME	Mild NPDR/CSME	2/60 NIP	6/36 PH 6/24	Ischemic	Mixed	Spongy	Spongy	298	540
Pencilamma	42	F	4	Type 2 OHA	Mild NPDR/CSME	Moderate NPDR/CSME	6/24 NIP	6/12 NIP	Diffuse	Focal	Spongy	Cysoid with SRD	540	448
Muthulaxmi	57	F	6	Type 2 OHA	Severe NPDR/CSME	Severe NPDR/CSME	6/12 NIP	6/24 NIP	Focal	Focal	Spongy	Spongy	563	268
Radhakrishnan	63	M	9	Type2 insulin	PDR/CSME	Severe NPDR/CSME	6/36 NIP	6/12 PH 6/9	Mixed	Focal	Spongy	Cystoid	589	484
Pandian	55	M	7	Type 2 OHA	Mild NPDR/CSME	Moderate NPDR/CSME	6/24 NIP	6/36 NIP	Focal	Diffuse	TPH	Spongy	496	554
Kamalamma	65	F	8	Type 2 OHA	Severe NPDR/CSME	PDR/CSME	6/12 PH 6/9	6/9 NIP	Focal	Mixed	Spongy	Cysoid with SRD	512	326
Arumugam	45	M	4	Type 2 OHA	Mild NPDR/CSME	Mild NPDR/CSME	6/36 PH6/12	6/36 PH 6/24	Diffuse	Focal	Cystoid	Spongy	536	482
Prema	69	F	9	Type2 insulin	Moderate NPDR/CSME	Moderate NPDR/CSME	6/24 PH 6/12	6/36 PH 6/18	Focal	Diffuse	Spongy	Spongy	214	461
Srinivasan	57	M	4	Type 2 OHA	Mild NPDR/CSME	Moderate NPDR/CSME	6/12 NIP	6/36 PH 6/24	Focal	Focal	Cystoid	Cystoid	593	547

Chennaiya	67	M	8	Type 2 OHA	Severe NPDR/CSME	Moderate NPDR/CSME	6/12 PH 6/9	6/24 PH 6/18	Focal	Diffuse	Spongy	Spongy	524	214
Vallikannu	36	F	10	Type 1	Moderate NPDR/CSME	Severe NPDR/CSME	6/9 NIP	6/18 NIP	Diffuse	Focal	Spongy	Cystoid	350	580
Karunakaran	39	M	12	Type 1	Severe NPDR/CSME	Moderate NPDR/CSME	6/12 NIP	6/12 PH 6/9	Focal	Focal	Spongy	Spongy	264	291
Shanti	63	F	6	Type2 insulin	Severe NPDR/CSME	Moderate NPDR/CSME	5/60 NIP	6/24NIP	Diffuse	Focal	VMT	Spongy	554	394
Gubendran	68	M	9	Type2 insulin	Severe NPDR/CSME	Severe NPDR/CSME	6/24NIP	4/60 PH6/60	Focal	Focal	Spongy	Cystoid	246	694
Gowri	59	F	8	Type 2 OHA	Moderate NPDR/CSME	Severe NPDR/CSME	6/36 PH6/18	5/60 NIP	Focal	Diffuse	Cystoid	Cystoid	451	490
Govindraj	72	M	14	Type2 insulin	Moderate NPDR/CSME	Moderate NPDR/CSME	6/36 PH6/12	6/36NIP	Diffuse	Mixed	Cysoid with SRD	Spongy	454	415
Perumal	74	M	16	Type2 insulin	Severe NPDR/CSME	Moderate NPDR/CSME	6/9NIP	6/36 PH 6/18	Focal	Mixed	Spongy	Spongy	332	424
Saraswati	53	F	7	Type 2 OHA	Moderate NPDR/CSME	Mild NPDR/CSME	6/12 PH 6/9	6/24 PH 6/18	Focal	Focal	Cysoid with SRD	Spongy	289	280
Balakrishnan	58	M	7	Type 2 OHA	Moderate NPDR/CSME	Moderate NPDR/CSME	4/60 PH 6/60	5/60 NIP	Mixed	Mixed	Spongy	Cystoid	756	487